ORGANIC SYNTHESES

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AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

Volume 47

1967

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QD 262 .O7 v.47 1967

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Library of Congress Catalog Card Number: 21–17747

PRINTED IN THE UNITED STATES OF AMERICA

NOMENCLATURE

Preparations appear in the alphabetical order of common names of the compounds. For convenience in surveying the literature concerning any preparation through *Chemical Abstracts* subject indexes, the *Chemical Abstracts* indexing name for each compound is given as a subtitle if it differs from the common name used as the title.

SUBMISSION OF PREPARATIONS

Chemists are invited to submit for publication in *Organic Syntheses* procedures for the preparation of compounds which are of general interest, as well as procedures which illustrate synthetic methods of general utility. It is fundamental to the usefulness of *Organic Syntheses* that submitted procedures represent optimum conditions, and the procedures should have been checked carefully by the submitters, not only for yield and physical properties of the products, but also for any hazards that may be involved. Full details of all manipulations should be described, and the **range** of yields should be reported rather than the maximum yield obtainable by an operator who has had considerable experience with the preparation. For each solid product the melting-point **range** should be reported, and for each liquid product the **range** of boiling point and refractive index should be included. In some instances, it is desirable to include additional physical properties of the product, such as ultraviolet, infrared, or nuclear magnetic resonance spectra. The methods of preparation or sources of the reactants should be described in notes, and the physical properties (such as boiling point, index of refraction, melting point) of the reactants should be included except where rather standard commercial grades are specified.

Procedures should be written in the style and format employed in the latest published volume of *Organic Syntheses*. Copies of

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the current style sheet may be obtained from the Secretary of the Editorial Board. In Section 3, **Methods of Preparation,** there should be described other practical methods for preparing the compound which have appeared in the literature. It is unnecessary to mention methods which have been published but are of no practical synthetic value. In Section 4, **Merits of the Preparation,** a statement should be made indicating why the preparation is published in *Organic Syntheses.* Among the obvious reasons for publication would be the novelty of the procedure, general scope of the synthetic method, specific interest in the compound or its use as an intermediate for preparing other compounds, convenience of the method, and improvement in yields. Three copies of each procedure should be submitted to the Secretary of the Editorial Board. It is sometimes helpful to the Board if there is an accompanying letter setting forth the features of the preparation which are of interest.

Additions, corrections, and improvements to the preparations previously published are welcomed and should be directed to the Secretary.

EDITOR'S PREFACE

For nearly five decades the basic style and format of *Organic Syntheses* have remained relatively constant. In the past ten years, however, the Editorial Board has made a major effort to make *Organic Syntheses* a living repository of modern synthetic organic chemistry. With the use of the solicitation program and the cooperation of our contributors, considerable progress has been made in portraying, in experimental terms, the renaissance which has occurred in synthetic organic chemistry in recent years. Insofar as possible it is our aim to have each preparation represent a new or improved general synthetic method, or a unique compound of major theoretical or practical importance. In connection with this objective it is also obvious that the Merits Section of each preparation deserves the careful attention of both the chemist who submits the preparation and the chemist who reads it.

Notable examples of general synthetic procedures in Volume 47 include the synthesis of *aromatic aldehydes* (from dichloromethyl methyl ether), *aliphatic aldehydes* (from alkyl halides and trimethylamine oxide and by oxidation of alcohols using dimethyl sulfoxide, dicyclohexylcarbodiimide, and pyridinum trifluoroacetate; the latter method is particularly useful since the conditions are so mild), *carbethoxycycloalkanones* (from sodium hydride, diethyl carbonate, and the cycloalkanone), *m-dialkylbenzenes* (from the *p*-isomer by isomerization with hydrogen fluoride and boron trifluoride), and the *deamination of amines* (by conversion to the nitrosoamide and thermolysis to the ester). Other general methods are represented by the synthesis of *1,1-difluoroolefins* (from sodium chlorodifluoroacetate, triphenyl phosphine, and an aldehyde or ketone), the *nitration of aromatic rings* (with nitronium tetrafluoroborate), the *reductive methylation* of aromatic nitro compounds (with formaldehyde and hydrogen), the synthesis of *dialkyl ketones* (from carboxylic acids and iron powder), and the preparation of *1-substituted cyclopropanols* (from the condensation of a 1,3-dichloro-2-propanol derivative and ethylmagnesium bromide catalyzed by ferric chloride). Useful syntheses based on carbanion chemistry include those of *α-phenyl esters* (by alkylation of ethyl phenylacetate with alkyl halides and sodium amide), *ketones* (by concurrent alkylation and cleavage of 2,4-pentanedione with a reactive alkyl halide and potassium carbonate), and *2,4-diketones* (from the dianion of 2,4-pentanedione and alkyl halides). Other general procedures include the preparation of *anhydrides* (from acids, phosgene, and triethylamine), the reduction of *organic halides* (using isopropyl alcohol and magnesium powder), and the preparation of *unsolvated Grignard reagents*. Two photolytic preparations (both of which can be generalized and illustrate the great utility of this technique) are those of *1,2-divinylcyclobutane* (from butadiene) and *cyclohexylidenecyclohexane* (from decarbonylation of the corresponding ketene dimer). The merits of the lithium aluminum hydride-aluminum chloride reagent are illuminated by the reduction of a ketal to a *β-hydroxyethyl ether* and by the synthesis of an *equatorial alcohol* from an alkylcyclohexanone.

Compounds of special interest whose preparation is described include *1,2,3-benzothiadiazole 1,1-dioxide* (a benzyne precursor under exceptionally mild conditions), *bis(1,3-diphenylimidazolidinylidene-2)* (whose chemistry is quite remarkable), *6-(dimethylamino)fulvene* (a useful intermediate for fused-ring nonbenzenoid aromatic compounds), *diphenylcyclopropenone* (the synthesis of which is a milestone in theoretical organic chemistry), *ketene di(2-methoxyethyl) acetal* (the easiest ketene acetal to prepare), *2-methylcyclopentane-1,3-dione* (a useful intermediate in steroid synthesis), and *2-phenyl-5-oxazolone* (an important intermediate in amino acid chemistry).

As always, the Editors express their appreciation to the many contributors who make *Organic Syntheses* possible. We are particularly grateful for the patience and understanding shown by these chemists during the seemingly interminable delays which often occur between the acceptance of a preparation and its publication. We continue to welcome any suggestions on form, content, and improvements by which *Organic Syntheses* can better serve organic chemists.

William D. Emmons

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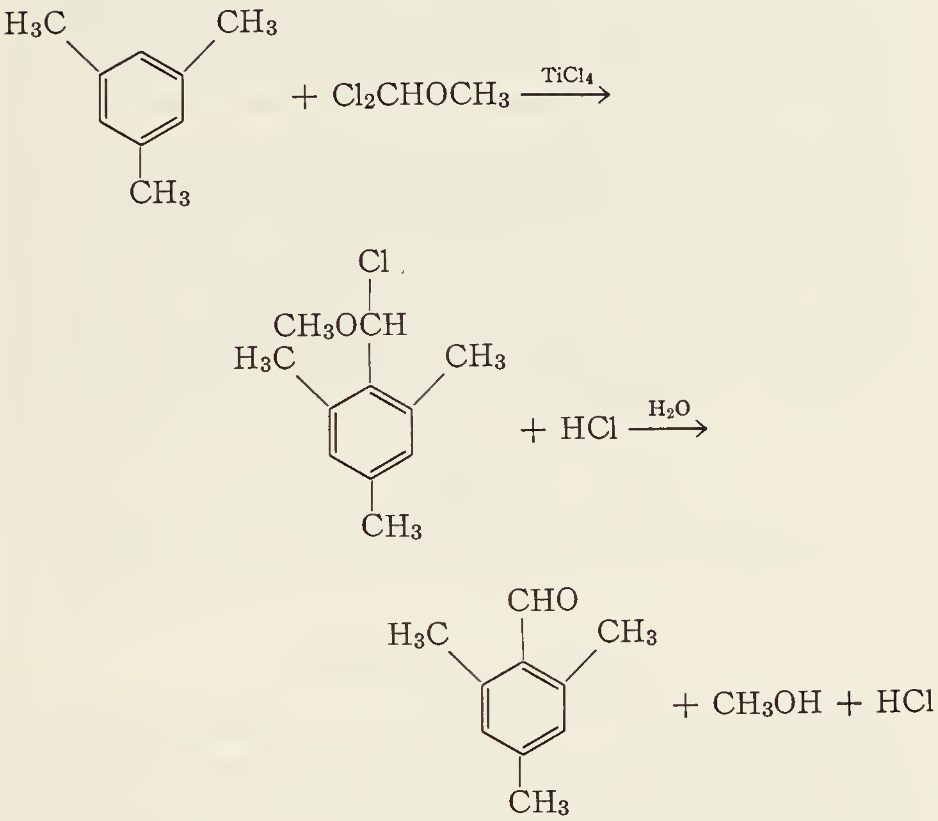
ORGANIC SYNTHESES

AROMATIC ALDEHYDES. MESITALDEHYDE

(Benzaldehyde, 2,4,6-trimethyl-)



Submitted by A. Rieche, H. Gross, and E. Höft[1]
Checked by G. N. Taylor and K. B. Wiberg

1. Procedure

A solution of 72 g. (0.60 mole) of mesitylene in 375 ml. of dry methylene chloride is placed in a 1-l. three-necked flask equipped with a reflux condenser, a stirrer, and a dropping funnel. The solution is cooled in an ice bath, and 190 g. (110 ml., 1.0 mole) of titanium tetrachloride is added over a period of 3 minutes. While the solution is stirred and cooled, 57.5 g. (0.5 mole) of dichloromethyl methyl ether[2] is added dropwise over a 25-

minute period. The reaction begins (as indicated by evolution of hydrogen chloride) when the first drop of chloro ether is added. After the addition is complete, the mixture is stirred for 5 minutes in the ice bath, for 30 minutes without cooling, and for 15 minutes at 35°.

The reaction mixture is poured into a separatory funnel containing about 0.5 kg. of crushed ice and is shaken thoroughly. The organic layer is separated, and the aqueous solution is extracted with two 50-ml. portions of methylene chloride. The combined organic solution is washed three times with 75-ml. portions of water. A crystal of hydroquinone is added to the methylene chloride solution (Note 1) which is then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue is distilled to give the crude product, b.p. 68–74° (0.9 mm.). After redistillation there is obtained 60–66 g. (81–89%) of mesitaldehyde; b.p. 113–115° (11 mm.), n^{20}_{D} 1.5538.

2. Note

1. Hydroquinone retards the autoxidation of the aldehyde.

3. Methods of Preparation

Mesitaldehyde may be prepared from mesitylmagnesium bromide by the reaction with orthoformate esters[3] or ethoxymethyleneaniline;[3] from acetylmesitylene by oxidation with potassium permanganate;[4] from mesitoyl chloride by reduction;[5] from mesityllithium by the reaction with iron pentacarbonyl;[6] and from mesitylene by treatment with formyl fluoride and boron trifluoride,[7] by treatment with carbon monoxide, hydrogen chloride, and aluminum chloride,[8] or by various applications of the Gatterman synthesis.[9–11]

4. Merits of the Preparation

The preparation of mesitaldehyde is an example of a generally applicable method for the preparation of aromatic aldehydes by treatment of aromatic compounds with dichloromethyl methyl ether.[12] Aldehydes derived from polynuclear aromatic compounds,[12,13] phenols,[14] phenol ethers,[12] and hetero-aromatic compounds [12] are also obtained using this procedure. In addition, colchicine derivatives have been formylated [15] by means of dichloromethyl methyl ether.

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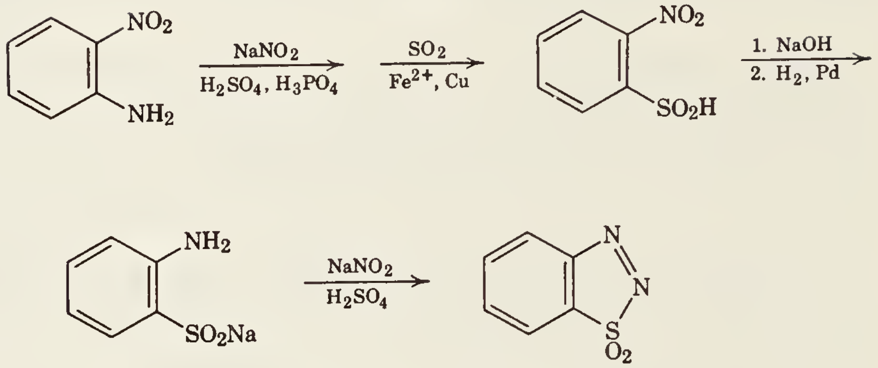
1,2,3-BENZOTHIADIAZOLE 1,1-DIOXIDE



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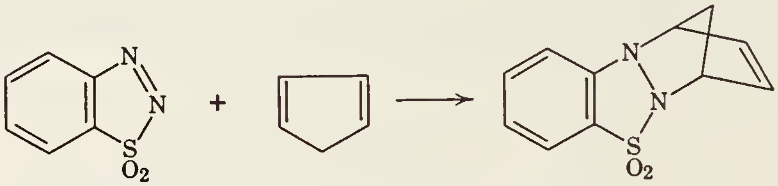


Submitted by G. Wittig and R. W. Hoffmann [1]
Checked by C. D. Smith, R. A. Clement, and B. C. McKusick

1. Procedure

A. *2-Nitrobenzenesulfinic acid* (*Note 1*). *Caution! This reaction should be done in a good hood because noxious fumes are released.*

2-Nitroaniline (13.8 g., 0.10 mole) (Note 2) is dissolved in a hot solution of 75 ml. of 96% sulfuric acid, 100 ml. of phosphoric acid (density 1.7), and 50 ml. of water in a 1-l. beaker. A stirrer and a thermometer are introduced into the mixture, and the beaker is immersed in an ice bath. A solution of 8.3 g. (0.12 mole) of sodium nitrite in 25 ml. of water is added dropwise to the well-stirred solution at such a rate that the temperature is maintained at 10–15°. Excess nitrite is destroyed by adding sulfamic acid in small portions (Note 3). The mixture is cooled to −10° in an ice-salt bath, and about 50 ml. of liquid sulfur dioxide

(Note 4) is poured into the well-stirred reaction. The product is immediately poured onto a mixture of 55.6 g. (0.20 mole) of $FeSO_4 \cdot 7\ H_2O$ and 1 g. of defatted copper powder in a wide 2-l. beaker. Nitrogen and excess sulfur dioxide bubble off with much foaming.

After 30 minutes the solid sulfinic acid is separated on a fritted-glass filter. The sulfinic acid is dissolved from the filter by a mixture of 750 ml. of ether and 750 ml. of methylene chloride. The solution is dried over calcium chloride and evaporated to dryness under reduced pressure (bath temperature 25°) (Note 5). The residue is suspended in 50 ml. of water, and small portions of dilute ammonia are added to the well-stirred suspension until it has a pH of 9 (Note 6). Insoluble impurities are separated by filtration, and 2-nitrobenzenesulfinic acid is precipitated from the filtrate by adding 5-ml. portions of 6*N* hydrochloric acid with cooling; the sulfinic acid precipitated by each portion of acid is separately collected on a Buchner funnel (Note 7). The acid, a pale yellow solid, is dried on a clay plate in a vacuum desiccator over potassium hydroxide pellets, m.p. 120–125° (dec.), weight 9.4–14.9 g. (50–80%). If the 2-nitrobenzenesulfinic acid is to be used for the hydrogenation of the next step high purity is required, and it is generally advisable to reprecipitate the acid once more in the same way (Note 8).

B. *Sodium 2-aminobenzenesulfinate.* 2-Nitrobenzenesulfinic acid (3.74 g., 0.020 mole) is suspended in 10 ml. of water, and sufficient 1*N* NaOH (about 20 ml.) is added to the well-stirred mixture to dissolve the acid and bring the pH to 9. Palladium oxide (0.2–1.0 g., Note 9) is suspended in 20 ml. of water in a 200-ml. glass hydrogenation bottle. The bottle is attached to a hydrogenation apparatus such as that of Adams and Voorhees,[2] and the suspension is shaken with hydrogen under a pressure of 1–3 atm. until the palladium oxide is reduced. The solution of 2-nitrobenzenesulfinic acid is added, and the mixture is shaken under a hydrogen pressure of 1–3 atm. The solution becomes completely decolorized in 2–6 hours, during which time about 95% of the calculated amount of hydrogen is absorbed. The catalyst is separated by filtration and washed with two 20-ml. portions of water, which are added to the filtrate. The filtrate, which may have a yellowish color, is evaporated to dryness under reduced pressure (bath temperature 45°). The residue, a white or light yellow solid, is sodium 2-aminobenzenesulfinate. After being dried in a desiccator over calcium chloride, it weighs 3.05–3.20 g. (85–89%).

C. *1,2,3-Benzothiadiazole 1,1-dioxide. Caution! 1,2,3-Benzothiadiazole 1,1-dioxide in the solid state can explode spontaneously, particularly on being warmed, jolted, or scratched. For most purposes it need not be isolated, but can be used in solutions, which are relatively safe. Any operations involving the solid material should be done very carefully, using good shielding.*

A solution of 1.43 g. (0.0080 mole) of sodium 2-aminobenzenesulfinate in the least possible amount of water is combined with a solution of 0.55 g. (0.0080 mole) of sodium nitrite in the least amount of water. A mixture of 16 ml. of 2*N* sulfuric acid and 22 ml. of glycerol is placed in a 250-ml. three-necked flask equipped with a dropping funnel, a low-temperature thermometer, and a stirrer, and the flask is immersed in a bath of acetone and dry ice. The stirred mixture is cooled to −15°, and the solution of sodium 2-aminobenzenesulfinate and sodium nitrite is added dropwise over a period of about 5 minutes; the cooling and rate of addition are such as to maintain the temperature at −15° ± 3°. The mixture is stirred for an additional 2 hours at this temperature, and 30 ml. of ether is added. The product is stirred vigorously for a few minutes and then allowed to warm to −6° with gentle stirring. The ether layer is decanted or transferred by means of a chilled pipet into a vessel cooled in a dry ice bath, and the reaction mixture is again cooled to −15°. In this way the reaction mixture is extracted with five 20-ml. portions of ether. After the last extraction the aqueous layer is frozen solid and the ether layer is poured off. The combined extracts are dried at −20°, first over calcium chloride and then over phosphorus pentoxide; a cold room at −20° is particularly convenient for this operation. The solution is transferred to a tared distillation flask immersed in an ice bath (Note 10), and the ether is removed by evaporation under reduced pressure. The flask is weighed rapidly and dried in a desiccator over phosphorus pentoxide at −20° (*Caution!* Notes 11, 12). The residue is 1,2,3-benzothiadiazole 1,1-dioxide in the form of yellow-brown needles; weight 0.77–1.04 g. (57–77%). It explodes between 45° and 60° (Note 13).

2. Notes

1. This is essentially the method of J. Lange.[3]

2. Technical material of Badische Anilin & Soda-Fabrik is satisfactory.

3. To detect nitrous acid, a drop of the mixture is diluted with water and tested with starch iodide paper.

4. It is convenient to condense sulfur dioxide from a cylinder in a calibrated trap cooled in a dry ice bath.

5. After the procedure had been checked, the submitters recommended the following time-saving modification. The methylene chloride-ether solution of the sulfinic acid is extracted with one 80-ml. portion and two 35-ml. portions of 2*N* sodium hydroxide solution. The extracts are combined and the sulfinic acid is precipitated with 5-ml. portions of 6*N* hydrochloric acid as described in the text.

6. An excess of ammonia leads to products that are contaminated with ammonium chloride.

7. In this way one avoids an excess of hydrochloric acid which, if it adheres to the product, causes its gradual decomposition.

8. The checkers dissolved the crude acid in the minimum amount of 2*N* sodium hydroxide (about 3 ml./g.) and reprecipitated it in 5 portions with 2*N* hydrochloric acid; recovery 75–85%. Alternatively, they added the acid to boiling ethyl acetate (9 ml./g.), added decolorizing carbon to the solution, boiled the mixture for 5 minutes, separated the carbon by filtration, and cooled the hot filtrate; recovery 45–55%. The checkers found no difference in the infrared spectra of material purified in the two ways, but recrystallized material was reduced more quickly by hydrogen.

9. The submitters used 0.2 g. of palladium oxide prepared by the method of Shriner and Adams[4] and required 2 hours for complete hydrogenation under a hydrogen pressure of 1 atm. The checkers used 1.0 g. of palladium oxide (75.7%) from

Engelhard Industries, 113 Astor Street, Newark, New Jersey, and required 4 hours for complete hydrogenation under a hydrogen pressure of 2–3 atm. Conditions should be chosen to give complete hydrogenation within 6 hours or colored by-products may be formed.

10. Not quite half of the flask should dip into the ice water or the layer of ice forming on the flask may be hard to remove.

11. 1,2,3-Benzothiadiazole 1,1-dioxide slowly decomposes even at 0°; hence it should always be used on the day on which it is made. For most purposes it is not necessary to isolate the dioxide; the ether solution can be used, or solutions in other solvents can be prepared by adding the other solvent and distilling off the ether under reduced pressure (bath temperature 0°). In this way larger amounts of the dioxide than are described in this procedure can be handled without danger.

12. 1,2,3-Benzothiadiazole 1,1-dioxide can be conveniently assayed and characterized without isolation by forming its adduct with cyclopentadiene.[5] The following procedure illustrates characterization; for assay the same procedure can be applied to an aliquot, with all amounts scaled down in proportion. The dried ether extract of 1,2,3-benzothiadiazole 1,1-dioxide prepared from 1.43 g. (0.0080 mole) of sodium 2-aminobenzenesulfinate is concentrated to about 20 ml. at 0°, and 20 ml. of acetonitrile at −20° is added. Twenty milliliters of cold, freshly prepared cyclopentadiene [6] is added. The mixture is kept overnight at −10° to 0°. Solvent and excess cyclopentadiene are removed by evaporation at 0° under reduced pressure to leave 1.20–1.28 g. (64–68% based on sodium 2-aminobenzenesulfinate) of crude 1:1 adduct, m.p. 87° (dec.). For purification it is dissolved in 20 ml. of methylene chloride, 70 ml. of ether is added, and the solution is kept at −70°. Adduct decomposing at 90° crystallizes; recovery is about 75%. From pure, crystalline 1, 2, 3-benzothiadiazole 1,1-dioxide the yield of adduct is 92–98%.

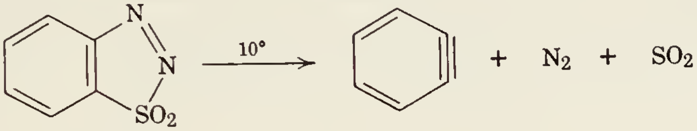
13. Purer product can be obtained by reducing 1,2,3-benzothiadiazole 1,1-dioxide with zinc and acetic acid to 1,2,3-benzothiadiazoline 1,1-dioxide, which is oxidized back with lead tetraacetate.[5]

3. Methods of Preparation

1,2,3-Benzothiadiazole 1,1-dioxide has been prepared only by the present method.[5]

4. Merits of the Preparation

1,2,3-Benzothiadiazole 1,1-dioxide decomposes smoothly in solution at 10° to give dehydrobenzene ("benzyne"), nitrogen, and sulfur dioxide.[5, 7] In this way, as well as by the thermal decomposition of benzenediazonium-2-carboxylate,[8, 9] it is possible to obtain dehydrobenzene in the absence of organometallic or strongly alkaline reagents; for this reason the choice of the reaction partner for dehydrobenzene is hardly limited at all. Compared to dry benzenediazonium-2-carboxylate, 1,2,3-benzothiadiazole 1,1-dioxide possesses the following advantages as a source of dehydrobenzene: the explosive compound does not need to be isolated and the decomposition temperature is lower. Solvent-wet benzenediazonium-2-carboxylate, being insoluble in most organic media, is less generally useful than 1,2,3-benzothiadiazole 1,1-dioxide but is more convenient to prepare.[9] Because of their special reaction conditions, other methods of obtaining dehydrobenzene without using an organometallic compound [10] are not so generally applicable. Earlier volumes of *Organic Syntheses* illustrate the preparation of dehydrobenzene by the action of magnesium on *o*-fluorobromobenzene [11] and a type of ring closure in which a dehydrobenzene is an intermediate.[12] Methods of generating dehydrobenzenes and the reactions of these reactive substances were recently reviewed.[13]



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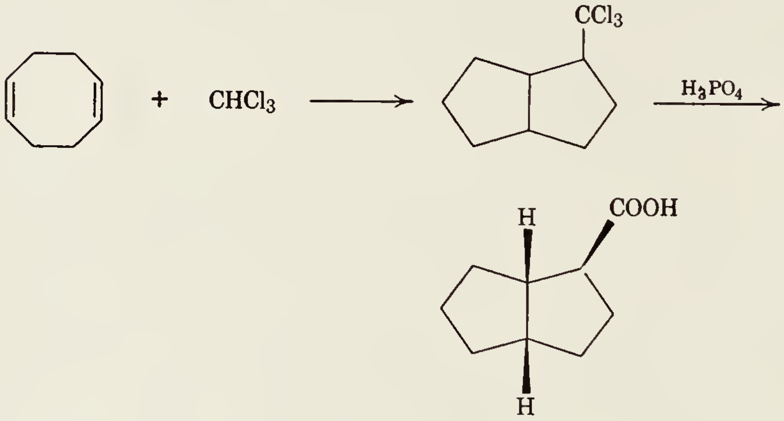
exo-cis-BICYCLO[3.3.0]OCTANE-2-CARBOXYLIC ACID

(1-Pentalenecarboxylic acid, octahydro-)



Submitted by R. Dowbenko[1]
Checked by E. J. Corey and B. W. Erickson

1. Procedure

A. *2-(Trichloromethyl)bicyclo[3.3.0]octane.* To a 5-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer are added 325 g. (3.0 moles) of *cis,cis*-1,5-cyclooctadiene (Note 1), 3 l. of chloroform (Note 2), and 14.6 g. (0.06 mole) of benzoyl peroxide. The resulting solution is stirred and refluxed (63–65°) on the steam bath (Note 3) for a total of 5 days. Four 7.3 g.-(0.03 mole-)portions of benzoyl peroxide are added, one on each consecutive day of reaction (Note 4). After a total of 5 days at reflux, the reaction mixture is cooled and washed with three 250-ml. portions of aqueous sodium bicarbonate (Note 5) and with 250 ml. of water, all the washes being discarded. The chloroform solution is dried with 30 g. of magnesium sulfate and filtered. The filtrate is distilled at atmospheric pressure using a short (8-in.) Vigreux column to collect 2760–2790 ml. of chloroform, b.p. 55–64°, which is discarded. The pressure is reduced and distillation continued to obtain two fractions: (1) b.p. 31° (47 mm.) to 65° (0.2 mm.), 300 g.; (2) b.p. 65–153° (0.2 mm.), 169 g. (Note 6). Fraction 2 is refractionated with the same Vigreux column to obtain 106–117 g. (approximately 35% based on unrecovered *cis,cis*-1,5-cyclooctadiene) of 2-(trichloromethyl)bicyclo[3.3.0]octane, b.p. 116–125° (5 mm.), $n^{25}\text{D}$ 1.5110–1.5115 (Note 7). The product is pure (by gas chromatography) (Note 8) and may be used in the next step.

B. *exo-cis-Bicyclo*[*3.3.0*]*octane-2-carboxylic acid.* A mixture of 100 g. (0.440 mole) of 2-(trichloromethyl)bicyclo[3.3.0]octane and 500 ml. of 85% phosphoric acid is put into a 1-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer. The mixture is stirred and heated at 150° for 16 hours, during which time it evolves hydrogen chloride and darkens. The product is then allowed to cool and is poured into a separatory funnel. One liter of water is added and the resulting mixture is extracted with four 250-ml. portions of ether. The combined ether extract is then extracted with four 250-ml. portions of 2% aqueous sodium hydroxide (Note 9), and the resulting alkaline extract is washed with 100 ml. of ether to remove any neutral material (Note 10). The alkaline extract is acidified (to pH 2–3) with concentrated hydrochloric acid, and the oil which precipitates is extracted with three 250-ml. portions of ether. The resulting ether extract is dried with 15 g. of magnesium sulfate, filtered, and evaporated at 50° (30 mm.). The residue is then distilled at reduced pressure to obtain 29–32 g.

(43–47%) of *exo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid, b.p. 91–96° (0.15 mm.), $n^{25}\text{D}$ 1.4839–1.4847 (Note 11).

2. Notes

1. The compound was obtained from Cities Service Research and Development Co., Petrochemical Development Department, Sixty Wall Tower, New York 5, New York. Analysis by gas chromatography showed it to be pure, and it was used without further purification.

2. Either technical or pure grade chloroform may be used.

3. It may also be refluxed with boiling chips without stirring. A heating mantle may be used in place of a steam bath.

4. The portions of peroxide may be added as such or, more conveniently and safely, as solutions in 25 ml. of chloroform over a period of 10–15 minutes.

5. It is important that all benzoic acid be removed by washing at this point because otherwise it will codistil with the product and will be difficult to separate by distillation.

6. Fraction 1 is discarded. If desired, it may be redistilled at atmospheric pressure to obtain, in addition to chloroform, 182 g. (1.68 moles) of *cis,cis*-1,5-cyclooctadiene, b.p. 145–157°.

7. The higher-boiling fraction, b.p. 129° (5 mm.) to 138° (0.2 mm.), amounts to 35–50 g. and contains at least four compounds.

8. A 2-ft. column of 20% UCON Polar 50 HB 5100 on Chromosorb W, 130°, retention time $5\frac{1}{4}$ minutes.

9. Because of the high acidity of the ether extract it is more convenient to use sodium hydroxide than sodium bicarbonate.

10. This ether wash may be combined with the main neutral fraction and distilled to obtain 29–30 g. (33–34%) of 2-(dichloromethylene)bicyclo[3.3.0]octane, b.p. 53–56° (0.1 mm.), $n^{25}\text{D}$ 1.5179–1.5182 (pure by gas chromatography) (column as in Note 8, 125°, retention time 4 minutes).

11. Analysis by gas chromatography shows the acid to be pure (column as in Note 8), retention time $4\frac{1}{2}$ minutes at 175°.

3. Methods of Preparation

exo-cis-Bicyclo[3.3.0]octane-2-carboxylic acid has been prepared from *cis*-bicyclo[3.3.0]-2-octanone cyanohydrin,[2] by Beckmann rearrangement of tetrahydro-*exo*-dicyclopentadiene-9-one oxime,[3] and by the present method.[4]

4. Merits of the Preparation

This two-step procedure appears to be by far the most convenient one for preparing *exo-cis*-bicyclo[3.3.0]octane-2-carboxylic acid from the readily available starting materials. The first step of the procedure is also illustrative of the method of obtaining 2-substituted bicyclo[3.3.0]octanes [4, 5] from *cis,cis*-1,5-cyclooctadiene.

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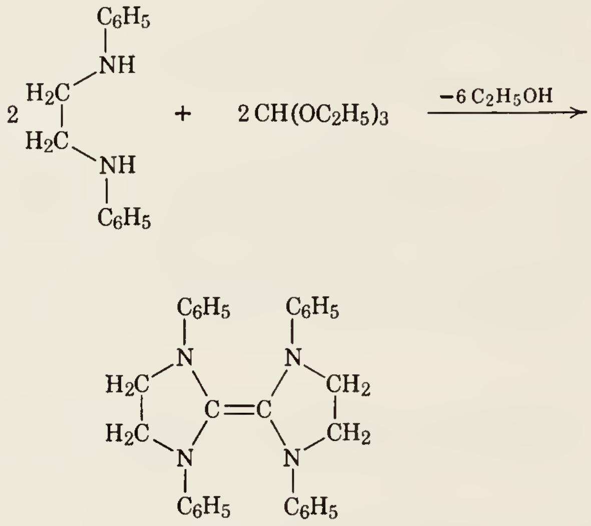
BIS(1,3-DIPHENYLIMIDAZOLIDINYLIDENE-2)

[$\Delta^{2,2'}$-Bis(1,3-diphenylimidazolidine)]



Submitted by H.-W. Wanzlick[1]
Checked by D. J. LaFollette and Ronald Breslow

1. Procedure

In a 250-ml. round-bottomed flask equipped with a gas-inlet tube and reflux condenser 20 g. (0.094 mole) of N,N′-diphenylethylenediamine (1,2-dianilinoethane) (Note 1) and 100 ml. of purified triethyl orthoformate (Note 2) are heated by an oil bath under nitrogen (Note 3) for 5 hours. The oil bath is maintained between 190° and 200°, and water is allowed to stand in the condenser. The water in the condenser begins to boil slowly, and the alcohol which is produced is allowed to escape (Note 4). The reaction product which crystallizes during the reaction is filtered after cooling and washed with ether. There is obtained 19–20 g. (91–95%) of product, m.p. 285° (dec.) (Note 5).

2. Notes

1. 1,2-Dianilinoethane, containing water of crystallization, is best dried by melting under vacuum.

2. Commercial material, distilled.

3. The nitrogen is dried by passing it through concentrated sulfuric acid. It must be nearly oxygen-free; otherwise 1,3-diphenylimidazolidinone-2 is formed, and its removal by recrystallization results in a decreased yield.

4. An air condenser may also be employed.

5. The melting range depends on the rate of decomposition during heating. The checkers observed that in an evacuated capillary there is darkening from 270° to 290°, and fairly sharp melting at 299–300°. The product is autoxidizable and is best stored under dry nitrogen. Preparations which have oxidized on standing may be purified by digesting and washing with methylene chloride.

3. Methods of Preparation

This amino olefin was first prepared by thermal elimination of chloroform from 1,3-diphenyl-2-trichlormethylimidazolidine,[2] and later by the procedure described here.[3, 4] It can also be made by treatment of 1,3-diphenylimidazolinium salts with strong bases.[5, 6]

4. Merits of the Preparation

The procedure described is the simplest one known. All other methods also employ 1,2-dianilinoethane as starting material. This method, however, converts it directly into the amino olefin in one step.

The preparative value of this compound lies in the surprising fact that bis(1,3-diphenylimidazolidinylidene-2) behaves in many reactions (*e.g.*, with aromatic aldehydes,[2, 7] and with carbon acids [2, 7–9]) as if it dissociated to form a "nucleophilic carbene." The hydrolytic cleavage of these derived imidazolidine derivatives makes possible the preparation of formyl compounds, so that the amino olefin can be considered as a potential carbonylation reagent. In many reactions it is not necessary to isolate the reagent, as it may be produced *in situ*.[10] It should be pointed out, however, that the reaction of the amino olefin with aldehydes and carbon acids does not actually involve prior dissociation to the carbene, but it is convenient, from a preparative point of view, to describe it in these terms.[6]

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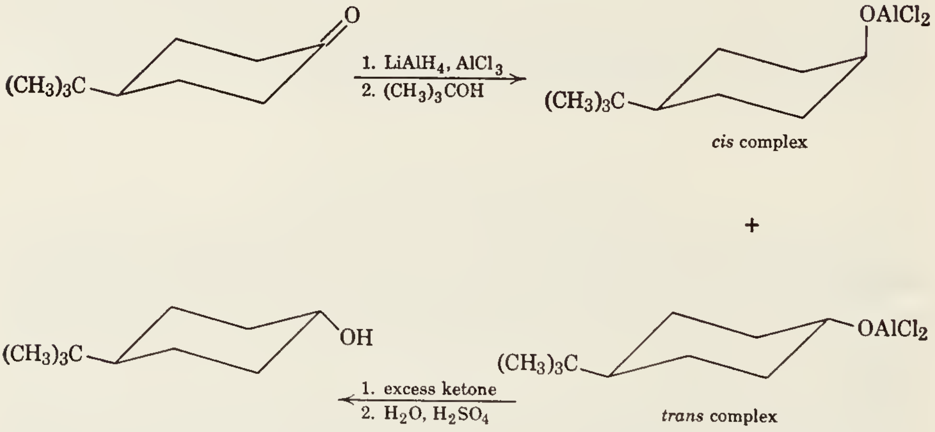
trans-4-*t*-BUTYLCYCLOHEXANOL

(Cyclohexanol, 4-*t*-butyl, *trans*-)



Submitted by E. L. Eliel, R. J. L. Martin, and D. Nasipuri[1]
Checked by E. J. Corey and Barbara Kaski

1. Procedure

In a 3-l. three-necked flask, equipped with a mercury-sealed Hershberg stirrer, a dropping funnel, and a reflux condenser protected with a calcium chloride tube, is placed 67 g. (0.5 mole) of powdered anhydrous aluminum chloride. The flask is cooled in an ice bath, 500 ml. of dry ether is slowly added from the dropping funnel, and the mixture is stirred for a few minutes. Meanwhile 5.5 g. of powdered lithium aluminum hydride (Note 1) is placed in a 1-l. flask fitted with a condenser, and 140 ml. of dry ether is added slowly from the top of the condenser with caution while the flask is kept cooled in ice. The mixture is gently refluxed for 30 minutes to effect, as far as possible, solution of the hydride. It is then cooled, and the resulting slurry (which consists of a suspension of lithium aluminum hydride in its solution) is transferred to the dropping funnel of the previous setup and is added to the ethereal solution of aluminum chloride with stirring within 10 minutes. After the addition is complete, the reaction mixture is stirred for an additional 30 minutes without cooling to complete the formation of the "mixed hydride."

A solution of 77.2 g. (0.5 mole) of 4-*t*-butylcyclohexanone (Note 2) in 500 ml. of dry ether is then placed in the dropping funnel and slowly added to the "mixed hydride" solution without much cooling so that gentle refluxing is maintained (Note 3). After addition of the ketone over a period of 45–60 minutes the reaction mixture is refluxed for 2 hours more to complete the reduction. The excess hydride is destroyed by the addition of 10 ml. of dry *t*-butanol, and the mixture is refluxed for an additional 30 minutes. 4-*t*-Butylcyclohexanone (3 g.) in 20 ml. of dry ether is then added to the reaction mixture, which is refluxed for 4 hours more and allowed to stand overnight (Notes 4, 5). The reaction mixture is cooled in an ice bath and decomposed by successive additions of 100 ml. of water and 250 ml. of 10% aqueous sulfuric acid. The ethereal layer is separated and the aqueous layer extracted once with 150 ml. of ether. The combined ether extracts are washed once with water and dried over anhydrous magnesium sulfate. The extract is filtered from magnesium sulfate and the ether removed by distillation on a steam bath. The residue, weighing 85–87 g., solidifies in the flask and on gas chromatographic analysis (see Note 5) is found to contain 96% *trans* alcohol, 0.8% *cis* alcohol, and 3.2% ketone.

The crude white product is dissolved in 150 ml. of hot petroleum ether (b.p. 60–70°). On cooling, it forms a solid cake which is transferred to a Buchner funnel and rinsed with small portions of cooled petroleum ether. The yield of product, m.p. 75–78°

(Note 6), is 57–61 g. (73–78%). It has an approximate composition of 99.3% *trans* alcohol, 0.3% *cis* alcohol, and 0.4% ketone. A further crop of 12 g. is obtained by concentration of the mother liquor. It contains less than 1% of the *cis* alcohol and the ketone and is sufficiently pure for most preparative purposes (Note 7).

2. Notes

1. The lithium aluminum hydride was obtained from Metal Hydrides Incorporated and was more than 95% pure. For calculation of the quantity of hydride required it was assumed that the purity was 95%.

2. 4-*t*-Butylcyclohexanone was supplied by the Dow Chemical Company.

3. The continuance of gentle refluxing as the last portion of the ketone is added assures that there is an excess of "mixed hydride" present.

4. It is not necessary to allow the reaction mixture to stand overnight, and it may be decomposed at this stage without any loss in purity.

5. At this stage the attainment of equilibrium can be checked by removing a 5-ml. aliquot from the reaction product and working it up in the same way as described in the preparation. The product is then analyzed by gas-liquid chromatography using a 20% Carbowax 20M on firebrick column at 150°. The features to note in the chromatogram are almost complete absence (less than 1%) of the *cis* isomer (second peak, disregarding initial solvent and *t*-butanol peaks) and the presence of some 4-*t*-butylcyclohexanone (first peak). The *trans* isomer constitutes the third peak with longest retention time.

6. The melting point of a highly purified sample[2] of *trans* alcohol is 82.5–83°.

7. Since the alcohol has a relatively high solubility in petroleum ether, the yield from the crystallization depends on the volume of solvent used. However, by concentrating the mother liquor the overall yield from the first and second crops of crystals varies from 74% to 94%.

3. Methods of Preparation

4-*t*-Butylcyclohexanol has been prepared from *p*-*t*-butylphenol by reduction under a variety of conditions.[3, 4] Winstein and Holness[5] prepared the pure *trans* alcohol from the commercial alcohol by repeated crystallization of the acid phthalate followed by saponification of the pure *trans* ester. Eliel and Ro[6] obtained 4-*t*-butylcyclohexanol containing 91% of the *trans* isomer by lithium aluminum hydride reduction of the ketone. Hückel and Kurz[7] reduced *p*-*t*-butylphenol with platinum oxide in acetic acid and then separated the isomers by column chromatography.

4. Merits of the Preparation

The procedure employs a readily available starting material and produces the pure *trans* isomer in high yield. The method described is an improvement on that used by Eliel and Rerick[2] in that it is not necessary to use a clear solution of lithium aluminum hydride in ether for the preparation of the "mixed hydride." It is not necessary to know the precise amount of lithium aluminum hydride used so long as a slight excess is present. The excess hydride is destroyed by adding *t*-butanol; the excess *t*-butanol has no effect on the subsequent equilibration and purification. The equilibration of the 4-*t*-butylcyclohexanol is effected by adding a small amount of 4-*t*-butylcyclohexanone.

The method is useful in the preparation of other equatorial alcohols.[2, 8]

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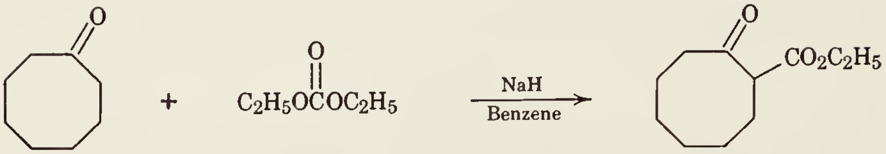
2-CARBETHOXYCYCLOOCTANONE

(2-Oxocyclooctanecarboxylic acid, ethyl ester)



Submitted by A. Paul Krapcho, Joseph Diamanti,
Charles Cayen, and Richard Bingham[1]
Checked by William G. Dauben and Charles Dale Poulter

1. Procedure

A 2-l. two-necked, round-bottomed flask equipped with a magnetic stirrer (Note 1) is fitted with a 250-ml. pressure-equalizing constant-rate dropping funnel and a condenser, the top of which is connected to a mercury trap to prevent the entrance of air during the reaction and for the detection of gas evolution. The dropping funnel is removed, and 35 g. (0.85 mole) of sodium hydride dispersed in mineral oil is added (Note 2). The mineral oil is removed by washing the dispersion four times with 100-ml. portions of benzene (Note 3). The benzene is removed with a pipet after the sodium hydride is allowed to settle (Note 4).

After most of the mineral oil has been removed, 400 ml. of benzene is added to the sodium hydride, followed by 71 g. (0.6 mole) of diethyl carbonate (Note 5). This mixture is heated to reflux, and a solution of 38 g. (0.3 mole) of cyclooctanone (Note 6) in 100 ml. of benzene is added dropwise from the dropping funnel over a period of 3–4 hours. After the addition is complete, this mixture is allowed to reflux until the evolution of hydrogen ceases (15–20 minutes).

When the reaction mixture has cooled to room temperature, 60 ml. of glacial acetic acid is added dropwise, and a heavy, pasty solid separates. Ice-cold water (about 200 ml.) is added dropwise, and the stirring is continued until all the solid material has gone into solution (Note 7). The benzene layer is separated, and the aqueous layer is extracted three times using 100-ml. portions of benzene. The combined benzene extracts are washed three times with 100-ml. portions of cold water. The benzene is removed by distillation at atmospheric pressure, and the excess diethyl carbonate is removed under water-pump pressure with gentle heating. The residual material is transferred to a 100-ml. distillation flask, and the fraction boiling at 85–87° (0.1 mm.) is collected. The yield of 2-carbethoxycyclooctanone is 54–56 g. (91–94%), $n^{25}\text{D}$ 1.4795–1.4800.

2. Notes

1. The checkers found that the agitation of the reaction mixture required later in this reaction is better achieved by use of a sealed mechanical stirrer.
2. The sodium hydride was obtained as a 58.6% dispersion in mineral oil from Metal Hydrides, Inc., Beverly, Massachusetts.
3. The benzene (Fisher certified reagent, thiophene free) was dried over potassium hydroxide and distilled from sodium metal.
4. By this procedure about 80–85% of the mineral oil was removed. Because some sodium hydride is lost in the pipetting procedure, an excess is initially employed.
5. The product supplied by Matheson, Coleman and Bell was used as received. Lower yields were obtained when a molar equivalent of diethyl carbonate was utilized, possibly because of self-condensation of the ketone.
6. The cyclooctanone was obtained from the Aldrich Chemical Co. and was utilized as received.
7. At this point the aqueous layer should be acidic, or more acetic acid should be added.

3. Methods of Preparation

The reaction of cyclooctanone with diethyl oxalate, followed by decarbonylation of the resulting glyoxylate, has been reported to yield 32% of 2-carbethoxycyclooctanone.[2] The reaction of cyclooctanone with sodium amide in ether, followed by the addition of diethyl carbonate, provided the product in 70% yield.[3]

The preparation of several medium- and large-sized 2-carbomethoxycycloalkanones has been accomplished by treatment of the cycloalkanone with sodium triphenylmethyl, followed by carbonation with dry ice, and esterification with diazomethane.[4] The yields are good but the procedure is laborious. The synthesis of 2-carbomethoxycyclooctanone via the Dieckmann cyclization of dimethyl azelate with sodium hydride yields 48% of this product when the procedure is carried out over a 9-day period.[5]

4. Merits of the Preparation

The reaction described is of general synthetic utility for the preparation of a variety of cyclic β-keto esters from the corresponding ketones. Using this procedure the 2-carbethoxycycloalkanones have been prepared from cyclononanone, cyclodecanone, and cyclododecanone in yields of 85%, 95%, and 90%, respectively. The procedure is simpler and gives much higher yields than other synthetic routes to these systems.

This procedure has been patterned after the method by which the carbethoxy group is introduced into a few alicyclic ketones[6] and several cyclic ketones. Cyclohexanone has been reported to yield 50% of 2-carbethoxycyclohexanone when treated with sodium hydride and diethyl carbonate using ether as the solvent.[7] The preparation of 2-carbethoxycycloheptanone using potassium *t*-butoxide and diethyl carbonate in benzene has been reported in 40% yield.[8] Jacob and Dev report an 80% yield of the latter compound using sodium hydride as the base.[9]

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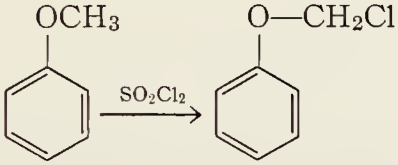
α-CHLOROANISOLE

(Chloromethyl phenyl ether)



Submitted by Charles S. Davis and Guy S. Lougheed [1]
Checked by William E. Parham, Wayland E. Noland,
and Edward E. Paschke

1. Procedure

Caution! This preparation requires the use of a good hood.

In a 2-l. three-necked flask fitted with an efficient reflux condenser, stirrer, and pressure-equalizing dropping funnel are placed 216 g. (2.0 moles) of anisole (Note 1) and 400 ml. of methylene chloride (Note 2). The reflux condenser is attached to a drying tower. The solution is brought to reflux temperature with a heating mantle, and 167 ml. (278 g., 2.06 moles) of sulfuryl chloride (Note 3) is added dropwise over a 3-hour period. When the addition is complete, heating is continued for an additional 15 hours (Note 4).

The reaction vessel is cooled to 30° and the reflux condenser replaced with a distillation head and condenser. The methylene chloride is removed by distillation, b.p. 35–55°. The residue is then transferred to a 500-ml. round-bottomed flask and distilled through a 30-cm. Vigreux column. The yield of α-chloroanisole is 266–271 g. (93–95%), b.p. 74–77° (13 mm.), n^{25}_{D} 1.5342 (Notes 5, 6, 7).

2. Notes

1. Anisole supplied by Eastman Organic Chemicals is satisfactory.

2. Methylene chloride (b.p. 39.5–40.5°) supplied by Matheson, Coleman and Bell is suitable.

3. Sulfuryl chloride (practical grade) supplied by Matheson, Coleman and Bell is satisfactory.

4. Shorter reflux times give poorer yields.

5. There is no forerun.

6. The literature boiling points are 88–90° (15 mm.) and 60–70° (4 mm.).[2, 3]

7. On gas chromatographic analysis the α-chloroanisole prepared by this method was found to be 90% pure (15% Ucon oil LB-550-x on Chromosorb W). The α-chloroanisole may be redistilled, b.p. 84–85° (20 mm.), through a 30-cm. Vigreux column to yield a material of 96% purity, $n^{25}\text{D}$ 1.5346.

3. Methods of Preparation

α-Chloroanisole has been prepared by the reaction of sodium phenoxymethanesulfonate with phosphorus pentachloride[2] and by the direct chlorination of anisole with light.[3] The procedure described here is essentially that of Bordwell and Pitt.[4]

4. Merits of the Preparation

The present method gives better yields and is a simpler procedure than those described previously. The ease of preparation of α-chloro ethers enables one to effectively remove a protecting methyl group from a phenol.[2] α-Chloroanisole is used to produce phenoxycarbene, a reactive intermediate in cyclopropane synthesis.[5]

1. Chemical Research Division, The Norwich Pharmacal Company, Norwich, New York.
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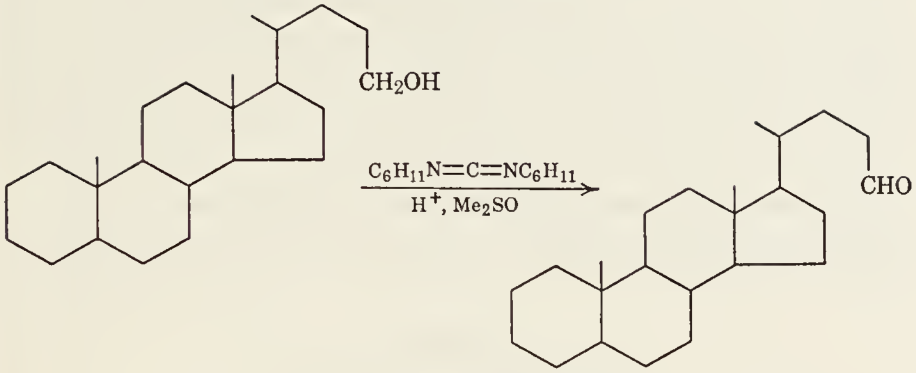
CHOLANE-24-AL



Submitted by John G. Moffatt[1]
Checked by Robert Fairweather and Ronald Breslow

1. Procedure

Cholane-24-ol (1.033 g., 3 mmoles) (Note 1) is dissolved by gentle warming in 10 ml. of anhydrous benzene (Note 2) in a 50-ml. flask, and 10 ml. of rigorously dried dimethyl sulfoxide (Note 3) is added. To the clear solution are added 0.24 ml. (3.0 mmoles) of anhydrous pyridine (Note 4), 0.12 ml. (1.5 mmoles) of distilled trifluoroacetic acid, and 1.85 g. (9 mmoles) of dicyclohexylcarbodiimide (Note 5), in that order. The flask is tightly stoppered and left at room temperature for 18 hours (Note 6). Benzene (30 ml.) is then added, and the crystalline dicyclohexylurea is removed by filtration (Note 7) and washed with benzene. The combined filtrates and washings are extracted three times with 50-ml. portions of water (Note 8) to remove the dimethyl sulfoxide. The organic layer is dried with sodium sulfate and evaporated to dryness under reduced pressure. There is obtained 2.12 g. of syrup which partially crystallizes. Thin-layer chromatography of this material (Note 9) shows a very intense spot of cholane-24-al, traces of starting material, and two compounds near the solvent front as well as excess carbodiimide (Note 9).

The crude product is dissolved in benzene-hexane (1:1) and applied to a column containing 125 g. of silicic acid (Note 10). Elution with the same solvent gives traces (less than 5 mg. each) of the two fast-moving components in fractions 2 and 4 (125-ml. fractions) and chromatographically pure cholane-24-al in fractions 5–8 (Note 11). Evaporation of the pooled fractions yields 870 mg. (84%) of the pure crystalline aldehyde, m.p. 102–104°. Recrystallization from 5 ml. of acetone raises the melting point to 103–104° (Note 12).

The compound gives a crystalline 2,4-dinitrophenylhydrazone, m.p. 163–164°, from ethanol.

2. Notes

1. Available from Aldrich Chemical Company.

2. Dried by storage over calcium hydride.

3. Dried by distillation under reduced pressure and storage for several days over Linde Molecular Sieves Type 4A.

4. Dried by distillation from, and storage over, calcium hydride.

5. The dry, crystalline material may be obtained from Aldrich Chemical Company. If the reagent is at all oily at room temperature, it should be distilled under reduced pressure, b.p. 140° (5 mm.).

6. Crystalline dicyclohexylurea (m.p. 234°) starts to separate after a short time. The checkers found a decrease in yield if this is allowed to run longer; a yield of 54% was found in a 22-hour reaction time.

7. Roughly 0.6–0.8 g. of the urea is usually obtained, m.p. 232–234°. The excess dicyclohexylcarbodiimide remains in the benzene. The oxidation is generally less satisfactory if less than 2.5 molar equivalents of carbodiimide is used.

8. Some further dicyclohexylurea tends to separate at the interface during the first extraction, and a clean separation of the layers near the interface is aided by mild centrifugation.

9. On Merck Silica G using benzene as the solvent and 5% ammonium molybdate in 10% sulfuric acid followed by brief heating at 150° to develop the spots. Under these conditions

cholane-24-al has an R_f of 0.76 while cholane-24-ol has R_f 0.19; dicyclohexylcarbodiimide streaks between 0.3 and 0.5.

10. Merck silica gel with 0.05–0.20 mm. particles obtained from Brinkman Instruments Inc. and packed in a 3-cm. diameter column under benzene-hexane (1:1).

11. The fractions were examined by thin-layer chromatography of 25–50 μl. aliquots as in Note 9. The checkers found that cholane-24-al is found in fractions 4–7.

12. The compound is very soluble in most organic solvents. In order to get a high recovery, it is necessary to complete the crystallization in the deep freeze. From aqueous ethanol the aldehyde crystallized in high yield as the hemihydrate, m.p. 95°.

3. Methods of Preparation

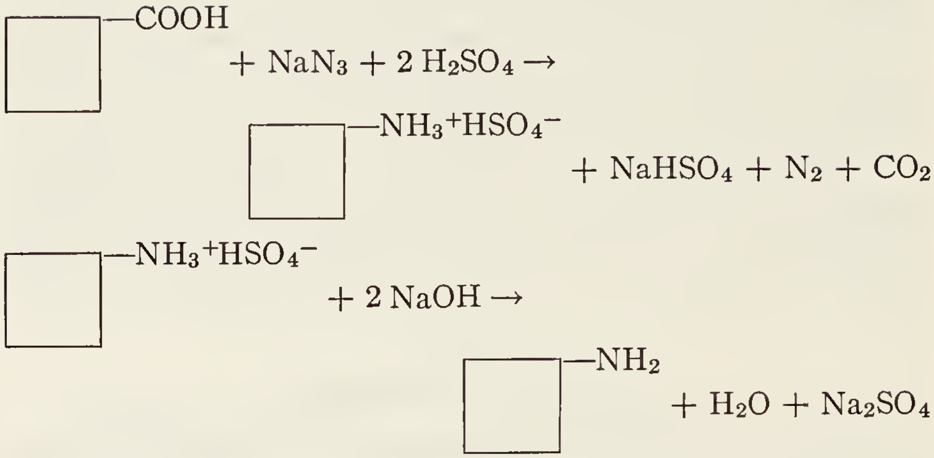
Cholane-24-al has not been previously synthesized by other methods.

4. Merits of the Preparation

The oxidation reaction described is a very general one that may be used for the preparation of both aldehydes and ketones[2] in high yield. The reaction conditions are extremely mild and only slightly acidic, thus allowing the preparation of otherwise very unstable compounds.[2] Of particular merit is the fact that the oxidation of primary alcohols stops selectively at the aldehyde and gives no traces of acidic products. Among the many different acids that have been examined as the proton source for this type of reaction,[2] pyridinium trifluoroacetate consistently gives the best results.

1. Syntex Institute for Molecular Biology, Palo Alto, California.
2. K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 87, 5661, 5670 (1965).

CYCLOBUTYLAMINE



Submitted by Newton W. Werner and Joseph Casanova, Jr.[1]
Checked by Donald Barth and Kenneth B. Wiberg

1. Procedure

Caution! The reaction should be carried out in a good hood because hydrazoic acid is very toxic. Care should also be taken in handling sodium azide.

In a 1-l. three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and powder funnel are placed 180 ml. of reagent grade chloroform, 16.0 g. (0.16 mole) of cyclobutanecarboxylic acid (Note 1), and 48 ml. of concentrated sulfuric acid. The flask is heated in an oil bath to 45–50°, and 20.0 g. (0.31 mole) of sodium azide (Note 2) is added over a period of 1.5 hours (Note 3). After the addition of sodium azide is complete, the reaction mixture is heated at 50° for 1.5 hours. The flask is cooled in an ice bath, and approximately 200 g. of crushed ice is added slowly. A solution of 100 g. of sodium hydroxide in 200 ml. of water is prepared, cooled to room temperature, and then added slowly to the reaction mixture until the pH of the mixture is approximately 12–13. The mixture is poured into a 2-l. three-necked, round-bottomed flask, the flask is set up for steam distillation, and about 2 l. of distillate is collected in a cooled receiver containing 90 ml. of 3*N* hydrochloric acid (Note 4). The water and chloroform are removed by distillation under reduced pressure (Note 5), and the amine hydrochloride is transferred to a 50 ml. round-bottomed flask with a few milliliters of water. A straight condenser is connected to the flask, and the flask is cooled in an ice bath. A slush is prepared by grinding potassium hydroxide pellets in a mortar and then adding a minimum volume of water. The slush is added in portions through the top of the condenser. After the mixture has become sufficiently basic, the amine appears as a separate phase. More potassium hydroxide pellets are added to dry the amine phase. The condenser is replaced by a heated, vacuum-jacketed Vigreux column equipped with a soda-lime tube, and the fraction having a boiling point of 79–83° is collected. The distillate is dried over potassium hydroxide pellets for 2 days. The liquid is decanted into a distilling flask containing a few potassium hydroxide pellets and distilled through the apparatus described above to give 7–9 g. (60–80%) of cyclobutylamine, b.p. 80.5–81.5°, $n^{25}\text{D}$ 1.4356 (Notes 6, 7).

2. Notes

1. Cyclobutanecarboxylic acid was purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin. A synthesis of the acid is described in *Org. Syntheses*, Coll. Vol. **3**, 213 (1955).
2. Eastman practical grade was used.
3. The sodium azide is added at such a rate that a gentle reflux of vapors in the powder funnel is maintained. After somewhat more than the theoretical amount of azide has been added, the rate of addition may be much more rapid.
4. The distillation should be carried out carefully at first until all the chloroform has distilled. A distilling adapter dipping just below the surface of the acid solution should be used in order to minimize loss of cyclobutylamine. Care must be taken that the basic solution in the distillation flask which still contains sodium azide does not come in contact with the hydrochloric acid solution in the receiver.

5. A water aspirator is sufficient.

6. Contact of the amine with the atmosphere should be avoided since the amine reacts with carbon dioxide.

7. The purity of the product was checked by vapor phase chromatography on a polyethylene glycol on Teflon column at 72°, 15 p.s.i., and a flow rate of 102 ml. of helium per minute. The sample appeared to be homogeneous, but, since the amine tails badly on the column, it is not possible to detect the presence of a small amount of water (less than 3%).

An n.m.r. spectrum of cyclobutylamine in carbon tetrachloride showed no resonance signals at less than 1 p.p.m. from tetramethylsilane. This suggests that no cyclopropylcarbinylamine was formed by rearrangement during the reaction.

3. Methods of Preparation

The preparation of cyclobutylamine from cyclobutanecarboxylic acid and hydrazoic acid has been reported previously.[2, 3] Cyclobutylamine has also been prepared by the Hofmann-type rearrangement of cyclobutanecarboxamide.[4–7]

4. Merits of the Preparation

This procedure permits the synthesis of cyclobutylamine from cyclobutanecarboxylic acid in one step and in high yield. The procedures involving the Hofmann rearrangement require the preparation of the amide from the acid and afford lower yields of the amine.

The interest in the synthesis of compounds containing the cyclobutyl ring system is due to the observation that reactions which are thought to proceed through cationic intermediates give rise to rearrangement products. For example, deamination of cyclobutylamine in aqueous solution gives cyclopropylcarbinol and allylcarbinol as well as cyclobutanol.[8] Recent investigations have been concerned with the exact nature of these cationic intermediates.[9, 10]

1. Department of Chemistry, California State College at Los Angeles, Los Angeles, California.

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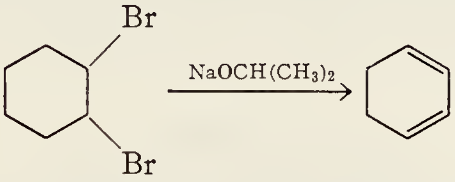
1,3-CYCLOHEXADIENE



Submitted by John P. Schaefer and Leland Endres[1]
Checked by R. J. Crawford and Peter Yates

1. Procedure

In a 3-l. three-necked, round-bottomed flask fitted with a mechanical stirrer and set up for a simple vacuum distillation are placed 500 ml. of triethylene glycol dimethyl ether (Note 1) and 300 ml. of isopropyl alcohol. Mechanical stirring is started, and 53.5 g. (2.23 moles) of sodium hydride in a mineral oil suspension is added in small portions. After the addition is complete, the remaining neck of the flask is fitted with a Y-tube to which is connected a two-holed rubber stopper containing a thermometer which reaches into the flask below the liquid level and a piece of glass tubing which is connected to a nitrogen tank. A pressure-equalizing dropping funnel containing 242 g. (1.00 mole) of 1,2-dibromocyclohexane (Note 2) is placed in the other arm of the Y-tube.

The temperature of the reaction flask is raised to 100–110°, and the receiving flask is cooled in a dry ice-isopropyl alcohol bath as a rapid stream of nitrogen is passed through the system. After most of the isopropyl alcohol has been removed by distillation (Note 3), the receiver is changed, and the system is evacuated by a water aspirator (Note 4). Dropwise addition of 1,2-dibromocyclohexane is begun, and the rate of addition is adjusted so that the temperature of the reaction mixture is maintained at 100–110° without external heating. The addition requires about 30 minutes; the reaction is terminated when distillation becomes very slow.

The distillate is washed four times with 200-ml. portions of water, and the organic layer is dried with anhydrous magnesium sulfate. The yield of 1,3-cyclohexadiene is 56 g. (70%) (Note 5). The diene can be separated from higher-boiling contaminants by a simple distillation at atmospheric pressure under nitrogen; b.p. 78–80°, yield 28–32 g. (35–40%) (Note 6).

2. Notes

1. 1,2-Bis(methoxyethoxy)ethane (triethylene glycol dimethyl ether) was obtained from Matheson, Coleman and Bell and used without further purification.

2. The 1,2-dibromocyclohexane was prepared by the method of Snyder and Brooks.[2] If the cyclohexene is cooled to *ca.* −30° with a dry ice-isopropyl alcohol bath and the bromine is not diluted, it is possible to run this preparation on a threefold scale in one-third of the recorded time. The product was always purified by the recommended procedure.

3. If the flow of nitrogen is rapid, the distillation can be completed in about 1 hour; otherwise the distillation is very slow.

4. A dry ice-isopropyl alcohol trap was inserted before the aspirator to catch any uncondensed product. The checkers also inserted a manometer between this trap and the aspirator, and maintained the pressure during the reaction at 130–170 mm. by careful adjustment of the regulator valve of the nitrogen cylinder.

5. If the temperature rises too high or the vacuum is not sufficient to flash out the diene as it forms, the product will be contaminated with small amounts of cyclohexene, benzene, and 1,4-cyclohexadiene.

6. The checkers found that distillation without the use of a nitrogen atmosphere gave 43–44 g. (54–55%) of product, b.p. 80–83°, of excellent purity as shown by n.m.r. spectroscopy.

3. Methods of Preparation

1,3-Cyclohexadiene has been prepared by dehydration of cyclohexen-3-ol,[3] by pyrolysis at 540° of the diacetate of cyclohexane-1,2-diol,[4] by dehydrobromination with quinoline of 3-bromocyclohexene,[5] by treating the ethyl ether of cyclohexen-3-ol with potassium bisulfate,[6, 7] by heating cyclohexene oxide with phthalic anhydride,[8] by treating cyclohexane-1,2-diol with concentrated sulfuric acid,[9] by treatment of 1,2-dibromocyclohexane with tributylamine,[10] with sodium hydroxide in ethylene glycol,[10] and with quinoline,[6] and by treatment of 3,6-dibromocyclohexene with sodium.[6]

4. Merits of the Preparation

Because of its convenience and simplicity this procedure is the method of choice for laboratory preparation of 1,3-cyclohexadiene. This olefin is an intermediate of some importance because it offers a route via the Diels-Alder reaction to a variety of bicyclic compounds.[4, 7, 10]

1. Department of Chemistry, The University of Arizona, Tucson, Arizona.
2. H. R. Snyder and L. A. Brooks, *Org. Syntheses*, Coll. Vol. **2**, 171 (1943).
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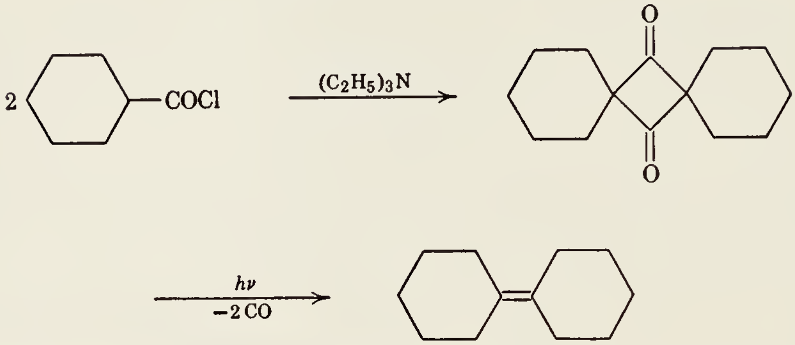
CYCLOHEXYLIDENECYCLOHEXANE

(Bicyclohexylidene)



Submitted by Nicholas J. Turro,[1] Peter A. Leermakers,[2]
and George F. Vesley [2]
Checked by Alex G. Fallis and Peter Yates

1. Procedure

A. *Dispiro[5.1.5.1]tetradecane-7,14-dione.* Cyclohexanecarbonyl chloride (Note 1) (30.0 g., 0.205 mole) and 250 ml. of dry benzene are placed in a three-necked, round-bottomed flask equipped with a stirrer, condenser, and dropping funnel. A nitrogen atmosphere is maintained in the system. Dry triethylamine (35.0 g., 0.35 mole) is slowly added, and the mixture is heated under reflux overnight. The amine hydrochloride is then filtered, and the filtrate is washed with dilute hydrochloric acid and with water. Solvent is removed on a steam bath, and the residue is recrystallized from ligroin-ethanol; yield 11–13 g. (49–58%), m.p. 161–162°.

B. *Cyclohexylidenecyclohexane.* In a Hanovia 450-watt immersion photochemical reactor (Note 2), equipped with a side arm attachment to monitor gas evolution, is placed 15 g. (0.068 mole) of dispiro[5.1.5.1]tetradecane-7,14-dione dissolved in 150 ml. of methylene chloride. The sample is irradiated, and carbon monoxide starts to evolve rapidly after a few minutes. Irradiation is continued until gas evolution has ceased, usually about 8–10 hours (Note 3). After the irradiation most of the solvent is removed on a steam bath. The residual oil is transferred to a sublimator. The sublimator, with the cold finger removed, is placed in a vacuum desiccator, and the system is evacuated to remove any remaining methylene chloride. The semisolid residue is then sublimed at 45° (1 mm.) to yield 7 g. (63%) of crude cyclohexylidenecyclohexane. The product after recrystallization from methanol weighs 5.5 g. (49%), m.p. 53–54°.

2. Notes

1. Cyclohexanecarbonyl chloride was obtained from Eastman Organic Chemicals.

2. The reactor, manufactured by the Hanovia Division of Engelhard Industries, consists of a water-jacketed Vycor well through which a stream of water is continuously passed. Since wavelengths shorter than 3000 Å are not needed, the immersion well may be made of Pyrex instead. Within the well is a No. 679A-36 450-watt medium-pressure mercury lamp, also manufactured by Hanovia, and a cylindrical Pyrex filter which surrounds the lamp. The well is placed in an appropriately shaped flask containing the solution to be irradiated. The flask is essentially cylindrical and is equipped with a side arm near the top through which gas can escape and be bubbled through a container of water. The flask is so designed that the liquid level is above the top of the lamp. The reaction vessel is quite similar to that shown in Fig. 1 (p. 65).

The same synthesis could be carried out in an ordinary flask using one or two sunlamps or sunlight, but the irradiation time would necessarily be much longer.

3. The system should be relatively free of oxygen during irradiation. Oxygen apparently combines with a photochemical intermediate to form cyclohexanone.[3] Under the conditions recommended in the procedure, oxygen is prevented from entering the system by the water trap which also serves as a monitor for gas evolution.

3. Methods of Preparation

Ethyl 1-bromocyclohexanecarboxylate, when treated with magnesium in anhydrous ether-benzene with subsequent addition of cyclohexanone, yields ethyl 1-(1-hydroxycyclohexyl)cyclohexanecarboxylate. Dehydration and saponification give rise to 1-(1-cyclohexenyl)cyclohexanecarboxylic acid, which upon decarboxylation at 195° yields cyclohexylidenecyclohexane in 8% overall yield, m.p. 54°.[4] This olefin has also been prepared by the debromination of 1,1′-dibromobicyclohexyl with zinc in acetic acid.[5]

The preparation of the dispiro[5.1.5.1]tetradecane-7,14-dione intermediate is essentially that of Walborsky and Buchman.[6]

4. Merits of the Preparation

The most obvious features of this synthesis are its simplicity and overall yield, which appear to be superior to those of any other published report. An important merit lies in the generality of the reaction, and the fact that it is an example of a reasonably large-scale photochemical preparation. Tetramethylethylene is readily produced from commercially available tetramethyl-1,3-cyclobutanedione by an identical route.[7]

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2. Hall Laboratory of Chemistry, Wesleyan University, Middletown, Connecticut.
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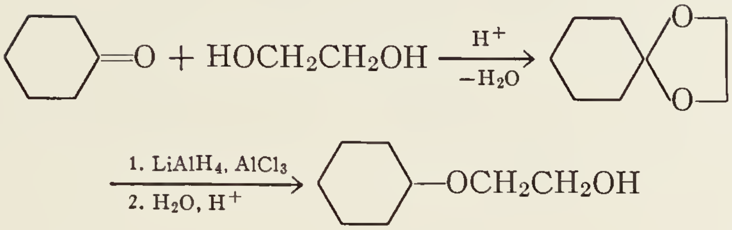
2-CYCLOHEXYLOXYETHANOL

[Ethanol, 2-(cyclohexyloxy)-]



Submitted by Ronald A. Daignault and E. L. Eliel[1]
Checked by J. R. Edman and B. C. McKusick

1. Procedure

A. *1,4-Dioxaspiro[4.5]decane.* A 1-l. round-bottomed flask is charged with 118 g. (1.20 moles) of cyclohexanone, 82 g. (1.32 moles) of 1,2-ethanediol, 250 ml. of reagent grade benzene, and 0.05 g. of *p*-toluenesulfonic acid monohydrate. The flask is attached to a water separator[2] under a reflux condenser fitted with a drying tube. A heating mantle is placed under the flask, and the reaction mixture is refluxed until close to the theoretical amount of water (21.6 ml.) has collected in the trap; this requires about 6 hours. The reaction mixture is cooled to room temperature, extracted successively with 200 ml. of 10% sodium hydroxide solution and five 100-ml. portions of water, dried over anhydrous potassium carbonate, and distilled through a 20-cm. Vigreux column. 1,4-Dioxaspiro[4.5]decane is obtained as a colorless liquid, b.p. 65–67° (13 mm.), weight 128–145 g. (75–85%), n^{25}_{D} 1.4565–1.4575.

B. *2-Cyclohexyloxyethanol.* A well-dried, 3-l. three-necked, round-bottomed flask is equipped with a stirrer, a pressure-equalizing dropping funnel, and a condenser to whose top is attached a calcium chloride drying tube. The flask is charged with 242 g. (1.81 moles) of anhydrous aluminum chloride powder and is immersed in an ice-salt bath. Anhydrous ether (25–50 ml.) is added dropwise through the dropping funnel, stirring is begun as soon as possible, and an additional 450–475 ml. of ether is added rapidly (total volume of ether added: 500 ml.). The mixture is stirred for approximately 30 minutes and becomes a light gray solution. During this period a mixture of 16.7 g. (0.44 mole) of lithium aluminum hydride and 500 ml. of anhydrous ether is vigorously stirred in a 1-l. round-bottomed flask under a nitrogen atmosphere (Note 1). The resulting suspension is added to the ethereal aluminum chloride solution through the dropping funnel. The resulting mixture, a gray slurry, is stirred for at least 30 minutes.

A solution of 125 g. (0.88 mole) of 1,4-dioxaspiro[4.5]decane in 200 ml. of anhydrous ether is added at a rate to cause gentle refluxing. The ice-salt bath is replaced by a steam bath, and the reaction mixture is refluxed for 3 hours. The calcium chloride drying tube is removed, and the steam bath is replaced by an ice bath. The excess hydride is carefully destroyed by adding water dropwise until hydrogen is no longer evolved; about 12 ml. of water is needed. This is followed by the more rapid addition of 1 l. of 10% sulfuric acid and then 400 ml. of water. This combination dissolves all the inorganic salts formed and results in the formation of two clear layers. The ether layer is separated in a 3-l. separatory funnel, and the aqueous layer is extracted with three 200-ml. portions of ether. The combined ethereal extracts are washed successively with 200 ml. of saturated sodium bicarbonate solution and 200 ml. of saturated brine. The ethereal solution is dried overnight over anhydrous potassium carbonate, filtered through a fluted filter paper, and concentrated by distillation on a steam bath. The residue, a pale yellow liquid weighing about 130 g., is distilled through a 20-cm. Vigreux column under reduced pressure. 2-Cyclohexyloxyethanol is obtained as a colorless liquid, b.p. 96–98° (13 mm.), weight 105–119 g. (83–94%), $n^{25}\text{D}$ 1.4600–1.4610.

2. Note

1. Most of the lithium aluminum hydride is in solution, but some is in suspension. When the humidity is below 35%, lithium

aluminum hydride can be weighed in air; otherwise the weighing should be done in a dry box. Although some workers pulverize lithium aluminum hydride before dissolving or suspending it in a liquid, *the checkers recommend that this not be done because it has led to several explosions in their laboratory.* The present procedure gives a fine suspension that generally passes through the stopcock of the dropping funnel without plugging it. A wooden stick or copper wire should be in readiness to clear the stopcock if it plugs up.

Twice the theoretical amount of lithium aluminum hydride is used, but this is necessary for the best yields.

3. Methods of Preparation

The method of preparing 1,4-dioxaspiro[4.5]decane is that of Salmi.[3] The methods used by Lorette and Howard [4] to prepare ketals are convenient for preparing 1,4-dioxaspiro[4.5]decane.

The present method of preparing 2-cyclohexyloxyethanol has been described before,[5] but on a smaller scale. Other β-hydroxy ethers [5] and β-hydroxy thio ethers [6] can be prepared by the same method. Hydrogenolysis of the C—O bond in acetals has also been reported [7] with diisobutylaluminum hydride; for example, 2-cyclohexyloxyethanol was obtained in 91% yield in this manner.

2-Cyclohexyloxyethanol has also been prepared by reduction of cyclohexyloxyacetic acid with lithium aluminum hydride [8] and by decomposition of cyclohexanone methanesulfonylhydrazone with sodium in ethylene glycol.[9]

4. Merits of the Preparation

The method described is more convenient than earlier methods of preparing 2-cyclohexyloxyethanol. It may be adapted to the preparation of other β-hydroxyethyl and γ-hydroxypropyl ethers [5] and the corresponding thio ethers.[6] Although ketals are resistant to reduction by lithium aluminum hydride alone, the presence of a Lewis acid facilitates C—O cleavage, presumably via an oxocarbonium ion,[10] as the procedure demonstrates.

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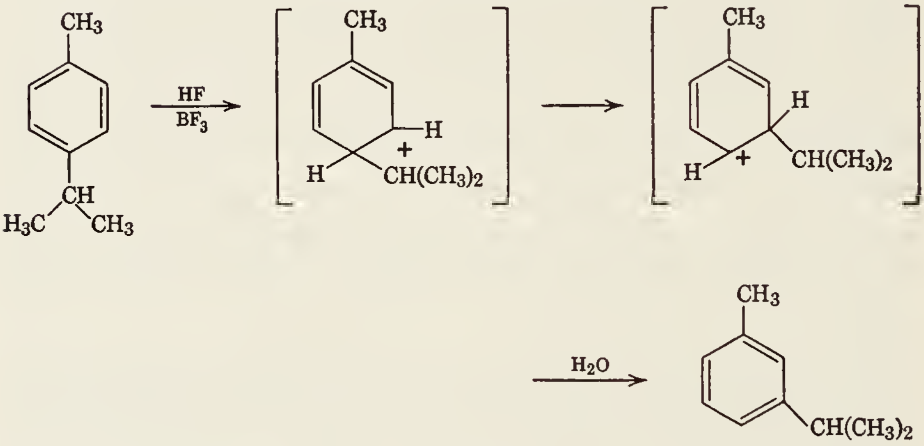
m-CYMENE

(*m*-Isopropyltoluene)



Submitted by D. E. Pearson, Robert D. Wysong, and J. M. Finkel[1]
Checked by Richard A. Haggard and W. D. Emmons

1. Procedure

Caution! It is necessary to carry out the entire operation including the workup in a well-ventilated hood. Rubber gloves and safety glasses should be worn (Note 1).

Anhydrous hydrogen fluoride (135 ml., approx. 7 moles) is liquefied by passing the gas through an 8-ft. spiral of ¼-in. I.D. copper tubing surrounded by an isopropyl alcohol-dry ice bath (Note 2). The liquid is delivered to a 500-ml. polyethylene squeeze bottle (Note 3) containing a magnetic stirring bar via a polyethylene tube inserted through the screw cap of the bottle. The squeeze bottle is contained in a 2-l. beaker and is surrounded by powdered dry ice (Note 4). After the hydrogen fluoride is collected, the cap and delivery tube are removed, and *p*-cymene (terpene-free, 67 g., 0.5 mole), precooled to −50° to −60°, just above the slush point, is added to the hydrogen fluoride. The cap and polyethylene tube assembly is now attached to deliver boron trifluoride. The delivery tube in this case dips below the surface of the hydrogen fluoride, the bottom layer. Boron trifluoride is bubbled through while the mixture is efficiently stirred with a magnetic stirrer (Note 5). A light orange color develops immediately, and the two layers become one in about 30 minutes (Note 6). Additional powdered dry ice must be added to the beaker during the boron trifluoride addition. The volume of the complex increases about 25%. After homogeneity is effected (in 30 minutes), a somewhat slower stream of boron trifluoride is added for an additional 30 minutes (Note 7). The delivery tube is replaced by a cap on the polyethylene bottle, the drying tube is removed, and the original side-arm tube is lowered to the bottom of the container. The cold reaction mixture is squirted, by squeezing the bottle, in a continuous small stream into a 4-l. beaker half-filled with cracked ice, vigorously hand-stirred. The bottle is rinsed, and the contents of the beaker are placed in a large separatory funnel. The upper colorless layer is separated, and the aqueous phase is extracted 3 times with 50-ml. portions of hexane. The combined organic layers are washed with three 50-ml. portions of water and dried overnight with anhydrous sodium sulfate under refrigeration (Note 8). The hexane solution at this point contains *m*-cymene with about 8% disproportionation impurities including toluene. The solution is fractionated through a 1-ft. helices-packed column, with the *m*-cymene at boiling point 173–176°, 50–54 g. (75–80%) being collected (Note 9).

2. Notes

1. In the event of accidental contact of hydrogen fluoride with the skin, the affected area must be washed immediately and

thoroughly with cold water. Additional treatment has been described.[2]

2. If one half the given quantity of hydrogen fluoride is used, all other factors being kept the same, the *m*-cymene formed contains as much as 5% of *p*-cymene.

3. A Nalgene "15–500" polyethylene bottle (Nalge Co., Rochester, New York) was used. The side arm coming off the shoulder of the bottle is kept well above the liquid level, the constricted tip removed, and the end of the tube connected to a drying tube containing clay plate chips impregnated with concentrated sulfuric acid.

A squeeze bottle can be simply made from a 500-ml. narrow-mouthed polyethylene bottle and polyethylene tubing. Holes in the bottle cap and shoulder are made with a sharp cork borer of the appropriate size to ensure a tight fit with the inserted tubing.

4. A polyethylene or copper foil loop 1 in. wide is placed between the squeeze bottle and the side of the beaker in such a position as to exclude the dry ice from the space and to provide a window to permit one to see that the liquid hydrogen fluoride fills the bottle to a premarked level. The frost on the beaker must be scraped off to allow inspection through the window.

5. The stirring motor is housed in a polyethylene bag to protect it from acid fumes.

6. Larger quantities of boron trifluoride are evolved from the drying tube at this point. During the first 30 minutes, boron trifluoride is added at a rate which gives a slow emanation of fuming vapor from the drying tube. The checkers found that the product was contaminated by *p*-cymene when inefficient stirring and slow boron trifluoride addition rates were employed (Note 7).

7. The checkers used a flowmeter to monitor boron trifluoride addition and found that an indicated addition rate of 1800 ml./min. (calibrated with air) for the first 5 minutes followed by an average rate of 600 ml./min. gave homogeneity in the prescribed time. A rate of 150 ml./min. was used for the second 30 minutes.

8. All glassware is rinsed with water immediately after use to prevent etching.

9. The product is analyzed by vapor phase chromatography using a 6-ft., $\frac{1}{4}$-in. O.D. copper tube, packed with 5% Bentone-34 (Wilkins Instrument Co.) and 0.5% XF-1150 (General Electric Silicone Products) on Diatoport-S (80–100 mesh) (F and M Co.); flow rate of helium 60 ml./min., oven temperature 85°. This column separates *m*-cymene (retention time 12 minutes) from *p*-cymene (retention time 10 minutes) but does not resolve the *ortho* isomer. The purity of the distilled *m*-cymene is above 98%.

3. Methods of Preparation

m-Cymene has been prepared from the Grignard reagent of *m*-bromotoluene and acetone followed by conversion of the carbinol to the chloride and reduction with sodium in liquid ammonia.[3] It also has been prepared from *m*-toluoyl chloride and excess methylmagnesium bromide followed by catalytic reduction of the olefin formed.[4] The best set of physical properties for the isomeric cymenes appears to be that of Birch and co-workers.[4] Many examples of Friedel-Crafts alkylation of toluene with propylene are described; apparently the best of them gives a 90% yield of cymenes containing 65–70% *m*-cymene.[5]

The method of preparation in this procedure is adapted from that of McCauley and Lien by which they obtained *m*-cymene in unstated yields.[6] The procedure has been altered to operate at −78° rather than −20°.

4. Merits of the Preparation

Aromatic hydrocarbons substituted by alkyl groups other than methyl are notorious for their tendency to disproportionate in Friedel-Crafts reactions. This tendency has previously limited the application of the isomerization of *para*-(or *ortho*-)dialkylbenzenes to the corresponding *meta* compounds. At the lower temperature of the present modification, disproportionation can be minimized.

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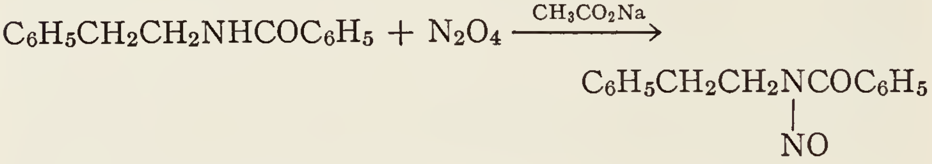
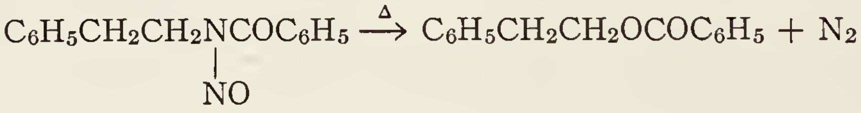
DEAMINATION OF AMINES. 2-PHENYLETHYL BENZOATE VIA THE NITROSOAMIDE DECOMPOSITION

(Benzoic acid, 2-phenylethyl ester)

$$C_6H_5CH_2CH_2NH_2 + C_6H_5COCl \xrightarrow{C_5H_5N} C_6H_5CH_2CH_2NHCOC_6H_5$$



$$C_6H_5CH_2CH_2NHCOC_6H_5 + N_2O_4 \xrightarrow{CH_3CO_2Na} C_6H_5CH_2CH_2\underset{\substack{|\\ NO}}{N}COC_6H_5$$



$$C_6H_5CH_2CH_2\underset{\substack{|\\ NO}}{N}COC_6H_5 \xrightarrow{\Delta} C_6H_5CH_2CH_2OCOC_6H_5 + N_2$$

Submitted by Emil White[1]
Checked by William G. Dauben and William C. Schwarzel

1. Procedure

Caution! Dinitrogen tetroxide is extremely toxic and should only be handled in an excellent hood.

A. *N-(2-Phenylethyl)benzamide.* To a solution of 12.1 g. (0.10 mole) of 2-phenylethylamine and 7.9 g. (0.10 mole) of pyridine in a 250-ml. Erlenmeyer flask immersed in an ice bath is added, slowly with stirring, 15.5 g. (0.11 mole) of benzoyl chloride. The resulting crystalline mixture is extracted with chloroform and the chloroform solution washed with water, 5% hydrochloric acid, 5% sodium hydroxide, water, and dried. The solvent is removed under reduced pressure to yield 20–22 g. (89–98%) of the crude amide, m.p. 100–110°, which is of sufficient purity for use in the next step. If desired, however, the crude product may be recrystallized from 95% ethanol, m.p. 115–116°.

B. *N-Nitroso-N-(2-phenylethyl)benzamide.* A solution of 10.4 g. (0.046 mole) of the crude N-(2-phenylethyl)benzamide, 7.36 g. (0.09 mole) of anhydrous sodium acetate, and 50 ml. of glacial acetic acid is placed in a 250-ml. Erlenmeyer flask equipped with a drying tube, and the mixture is cooled to the crystallization point of the acetic acid (Note 1). A solution of dinitrogen tetroxide (Notes 2, 3) in glacial acetic acid (85 ml. of a solution approximately $1M$ in N_2O_4) is then added with stirring. The reaction mixture is allowed to warm to about 15° (15 minutes), and then it is poured into a mixture of ice and water. The yellow solid nitroso derivative is dissolved in 75 ml. of carbon tetrachloride, and this solution is washed with 5% sodium bicarbonate, water, and dried. The solution is used directly in the next step.

If the nitroso derivative is desired, the yellow solid is separated by filtration, washed with water, 5% sodium bicarbonate solution, water, and dried under reduced pressure at room temperature. The solid is recrystallized from ether to give yellow needles of pure nitrosoamide; yield 7.5 g. (64%), m.p. 57–58° (dec.).

C. *2-Phenylethyl benzoate.* The carbon tetrachloride solution of N-nitroso-N-(2-phenylethyl)benzamide (Note 4) and 0.1 g. of sodium carbonate (Note 5) are placed in a 200-ml. round-bottomed flask equipped with a condenser, and the mixture is heated under reflux for 24 hours. The evolution of nitrogen ceases, and the yellow color of the nitrosoamide disappears near the end of this period. The solution is washed with 5% sodium hydroxide solution, water, and dried. The solvent is removed under reduced pressure and the 2-phenylethyl benzoate distilled; b.p. 138–142° (1 mm.), yield 5.8–6.1 g. [56–59% based on N-(2-phenylethyl)benzamide].

2. Notes

1. Carbon tetrachloride, methylene chloride, and other solvents may be used in this reaction. In these cases it is profitable to cool the reaction mixture to −40° or lower and then allow the mixture to warm to 10° after the dinitrogen tetroxide has been added.

2. Dinitrogen tetroxide (nitrogen dioxide) is available from the Matheson Company, Inc., East Rutherford, New Jersey.

3. Dinitrogen tetroxide is a *poisonous gas* and should only be handled in a well-ventilated hood. The boiling point of dinitrogen tetroxide is 21°, and it is convenient to condense a given volume (or weight, density = 1.5 g./ml. at 0°) from a cylinder of dinitrogen tetroxide and to pour the liquid into the required amount of solvent, or into the reaction mixture directly at temperatures below *ca.* −20°. Impure dinitrogen tetroxide, which is green because of the presence of lower oxides of nitrogen, may also be used.

4. Any nonreactive solvent may be used, but excessive temperatures favor the concurrent elimination reaction.

5. The sodium carbonate may be omitted if it is desired to titrate the acid formed in the reaction. The carbonate prevents denitrosation (observed in a few cases).

3. Methods of Preparation

The nitrosation of amides may also be carried out with nitrosyl chloride.[2] Related methods of deamination of aliphatic amines are the triazene[3] and nitrous acid methods.[4]

4. Merits of the Preparation

Dinitrogen tetroxide is the most versatile of the nitrosating reagents and, in addition, it is readily available. The nitrosoamide method of deamination gives far superior yields and much less skeletal isomerization than the nitrous acid method (which is essentially limited to aqueous media), and it leads to a greater retention of optical activity than the triazene method.[3]

In general, the nitrosoamide decomposition proceeds with retention of configuration.[5, 6]

The method outlined here works well for amides of primary carbinamines. For amides of secondary carbinamines, lower temperatures must be used, and solvents such as methylene chloride are used in place of the acetic acid (the amide need not be completely soluble in the solvent); the procedure of White and Aufdermarsh[5] used for a trimethylacetamide is recommended in such a case. Nitrosoamides of tertiary carbinamines are very unstable, and the "salt method" of preparation is suggested for these compounds.[6]

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DICHLOROMETHYL METHYL ETHER

$$HCOOCH_3 + PCl_5 \longrightarrow Cl_2CHOCH_3 + POCl_3$$

Submitted by H. Gross, A. Rieche, E. Höft, and E. Beyer[1]
Checked by G. N. Taylor and K. B. Wiberg

1. Procedure

In a 2-l. three-necked flask equipped with a stirrer, a reflux condenser, and a dropping funnel (Note 1) 832 g. (4.0 moles) of phosphorus pentachloride is stirred with 250 ml. of phosphorus oxychloride (Note 2). To this is added with stirring 264 g. (272 ml., 4.4 moles) of methyl formate (Note 3). During the addition the reaction vessel is cooled in an ice bath to maintain a reaction temperature of 10–20°. The addition requires about 1.75 hours. When the addition is complete, the solution is stirred at a temperature under 30° until all the phosphorus pentachloride has dissolved (about 1 hour). Then the stirrer is removed, the reflux condenser is replaced by a distilling head, and the reaction mixture is distilled under a pressure of 80–120 mm. with a bath temperature of 50–65° (Note 4). During the distillation the receiver is cooled to −10° to −20° by an ice-salt bath.

The material which is collected is redistilled through a 90-cm. vacuum-jacketed column packed with glass beads (5 mm.) using a 1:10 reflux ratio. The fraction, b.p. 80–100°, is redistilled through the same column to give 353–386 g. (77–84%) of dichloromethyl methyl ether, b.p. 82–85.5°, n^{20}_{D} 1.4303 (Note 5).

2. Notes

1. The reflux condenser and dropping funnel must be provided with calcium chloride tubes.
2. Phosphorus oxychloride serves only as a suspension medium for phosphorus pentachloride and makes possible a homogeneous reaction. The phosphorus oxychloride obtained during workup may be recycled in this preparation.
3. Commercial methyl formate was dried over sodium sulfate and used without special purification.
4. If it is not first distilled under reduced pressure, extensive decomposition will occur during fractional distillation.
5. The product must be protected from moisture when stored.

3. Methods of Preparation

Dichloromethyl methyl ether has been prepared by the chlorination of chlorodimethyl ether in the liquid [2–4] or gas phase,[5] by the reaction of chlorodimethyl ether with sulfuryl chloride and benzoyl peroxide,[6, 7] and by the treatment of methyl formate with phosphorus pentachloride.[8–10]

4. Merits of the Preparation

Dichloromethyl methyl ether may be employed preparatively in various ways. Thus it effects the replacement of carbonyl and hydroxyl oxygens by chlorine,[11] and may be used in the preparation of α-acetochlorosugars [12] and acid chlorides, particularly those derived from acetylated monocarboxylic acid sugars [12, 13] and acetylated amino acids.[14] In addition, the *ortho* derivatives of formic acid may be prepared from dichloromethyl methyl ether.[15] With aromatic compounds, dichloromethyl methyl ether reacts under Friedel-Crafts conditions followed by hydrolysis to give the corresponding aromatic aldehydes.[10, 16, 17]

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β,β-DIFLUOROSTYRENE

(1,1-Difluoro-2-phenylethylene)

$$\mathrm{C_6H_5CHO + (C_6H_5)_3P + ClF_2CCO_2Na \longrightarrow C_6H_5CH{=}CF_2 + CO_2 + NaCl + (C_6H_5)_3PO}$$

Submitted by Samuel A. Fuqua,[1] Warren G. Duncan,[2]
and Robert M. Silverstein [2]
Checked by John J. Miller, Herbert Aschkenasy,
and William D. Emmons

1. Procedure

In a 250-ml. two-necked flask fitted with a reflux condenser, a drying tube, a magnetic stirrer, and a heated dropping funnel with a pressure-equalizing side arm (Note 1) are placed 23.1 g.

(0.088 mole) of triphenylphosphine, 8.5 g. (0.081 mole) of benzaldehyde, and 10 ml. of anhydrous 2,2′-dimethoxydiethyl ether (diglyme) (Note 2). A solution of 18.3 g. (0.12 mole) of dry sodium chlorodifluoroacetate (Note 3) is prepared by stirring the finely divided salt in 50 ml. of anhydrous diglyme at 70° for about 5 minutes. This warm solution is placed in the dropping funnel which is heated to 60°. The system is purged with dry nitrogen. The solution in the flask is stirred and heated in an oil bath held at 160°, while the contents of the dropping funnel are added dropwise over a period of 1.5–2 hours (Note 4). The diglyme and product are flash-distilled at 1 mm. and a bath temperature of 100° into a receiver cooled with dry ice. The distillate is fractionated through a spinning-band column (18 in. × 6 mm. I.D.); the yield of product collected at a head temperature of 52–54° (40 mm.) is 7.6–8.9 g. (67–79%) (Note 5), $n^{20}\text{D}$ 1.4939 (Note 6).

2. Notes

1. All glassware is oven-dried. The dropping funnel is wrapped with heating tape, and a thermometer is inserted between the funnel and the tape.

2. Triphenylphosphine is available from M and T Chemicals, Inc. Benzaldehyde is distilled immediately before use. Diglyme is refluxed for 4 hours over calcium hydride and distilled under reduced pressure.

3. Sodium chlorodifluoroacetate is prepared from chlorodifluoroacetic acid (K & K Laboratories) as follows: To a cooled, stirred solution of 60.7 g. (1.52 moles) of sodium hydroxide in 700 ml. of methanol is slowly added a solution of 198 g. (1.52 moles) of chlorodifluoroacetic acid in 300 ml. of methanol, the temperature being kept below 40°. The methanol is removed under reduced pressure at 40°. The salt, which is pulverized and dried overnight at room temperature at 1 mm., is obtained in essentially quantitative yield. The salt is again dried in the same way immediately before use.

4. During the development of this procedure, evolution of carbon dioxide was monitored with a wet-test meter. At the bath temperature given (160°), sodium chlorodifluoroacetate

eliminates carbon dioxide as rapidly as it is added over a period of 1.5–2 hours. If the bath temperature is allowed to drop, there is danger of buildup of sodium chlorodifluoroacetate followed by violent exothermic decomposition. Addition of the sodium chlorodifluoroacetate solution should not be started until the flask contents are equilibrated with the oil bath.

It is quite feasible to run the reaction at a bath temperature of 90–95° by adding all reagents to the flask initially; a quantitative evolution of carbon dioxide occurs over a period of about 18 hours. The reaction can also be carried out in refluxing 1,2-dimethoxyethane (Arapahoe Chemicals, Inc.) over a period of about 50 hours (yield 40–55%), or in triethylene glycol dimethyl ether (Ansul Chemical Company) at a bath temperature of 160° over a period of 2 hours (yield 64%).

5. The distilled product gave a single symmetrical peak on gas chromatography under the following conditions: 25% LAC on Chromosorb W, 6 ft. × $\frac{1}{4}$ in., 110°, helium flow 41 ml./min., elution time 14.2 minutes. The checkers used LB 5-50 on Fluoropak 80 and obtained a single peak. Gas chromatography of the flash distillate before fractionation showed an actual yield of 10.6 g. (95%). The product fumes in moist air, and some etching of glass containers was noted. This is presumably due to elimination of hydrogen fluoride. Samples in open glass containers deposit a small amount of solid on standing; the solid is probably a product of the glass-hydrogen fluoride reaction.

6. Care must be taken to clean and dry the refractometer prisms before and after use in order to prevent etching of the prisms.

3. Methods of Preparation

The literature preparation[3] of β,β-difluorostyrene consists of seven steps from sodium difluoroacetate, the last step involving pyrolysis at 600°; the overall yield was 5%.

4. Merits of the Preparation

The method described is a general synthesis for compounds containing the —CH=CF_2 moiety. There is no other simple general route to such compounds. Aromatic, aliphatic, and heterocyclic aldehydes to which this procedure has been applied are: *p*-fluorobenzaldehyde (65%), *p*-methoxybenzaldehyde (60%), heptanal (43–51%), and furfural (75%).[4] The method is also applicable to ketones.[5]

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1. Deceased.
2. Stanford Research Institute, Menlo Park, California.
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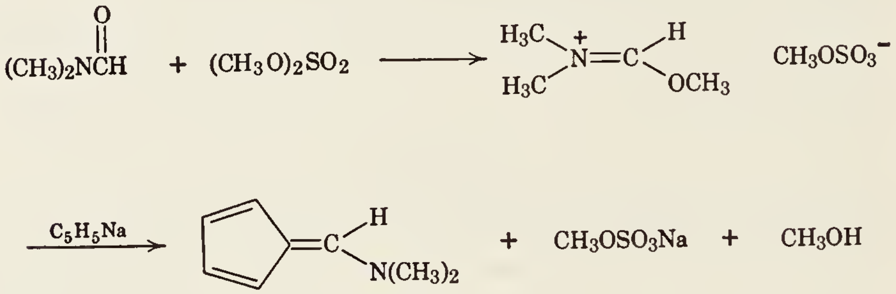
6-(DIMETHYLAMINO)FULVENE



Submitted by K. Hafner, K. H. Vöpel, G. Ploss, and C. König[1]
Checked by S. S. Olin and Ronald Breslow

1. Procedure

A. *N,N-Dimethylformamide-dimethyl sulfate complex.* In a 500-ml. four-necked flask equipped with mechanical stirrer, reflux condenser with calcium chloride drying tube, dropping funnel, and thermometer is placed 73 g. (1.0 mole) of dimethylformamide, and 126 g. (1.0 mole) of dimethyl sulfate is added dropwise with stirring at 50–60° (Note 1). After the addition is complete, the mixture is heated for another 2 hours at 70–80°. The dimethylformamide complex forms as a viscous, colorless or pale yellow ether-insoluble oil.

B. *6-(Dimethylamino)fulvene.* A 1-l. four-necked flask is equipped with mechanical stirrer, dropping funnel with calcium chloride drying tube, thermometer, and nitrogen delivery apparatus (Note 2). The flask is flushed with dry nitrogen, and in it is placed 1.0 mole of cyclopentadienylsodium[2] in 700 ml. of tetrahydrofuran (Note 3). The dimethylformamide-dimethyl sulfate complex prepared above is transferred to the dropping funnel and added slowly with stirring under nitrogen to the cyclopentadienylsodium at −10° (ice-salt bath). During the addition the temperature is kept below −5°. After the addition is complete, the mixture is stirred at 20° for 2 hours. The solution is filtered (with suction) from the precipitated sodium methyl sulfate, which is washed with another 200 ml. of tetrahydrofuran, and the combined tetrahydrofuran solutions are concentrated under reduced pressure. The residue is a dark brown oil which solidifies on cooling.

The crude product is crystallized after treatment with activated carbon from *ca.* 1.5 l. of petroleum ether (b.p. 60–80°) or 800 ml. of cyclohexane. From the orange-yellow solution 84 g. (69%) of 6-(dimethylamino)fulvene separates in yellow leaflets, m.p. 67–68° (Note 4). Concentration of the filtrate and further recrystallization of the residue from petroleum ether or cyclohexane gives an additional 8 g. of product. The combined yield is 92 g. (76%).

2. Notes

1. Dimethylformamide and dimethyl sulfate must be purified by distillation in the absence of moisture.

2. The nitrogen delivery apparatus has been completely described.[2]

3. Air and moisture must be carefully excluded from the reactants during the course of this preparation.

4. 6-(Dimethylamino)fulvene is light-sensitive and is stored in brown bottles.

3. Methods of Preparation

N,N-Dimethylaminoethoxymethylium fluoborate[3] can be used instead of N,N-dimethylaminomethoxymethylium methyl sulfate[4] to prepare 6-(dimethylamino)fulvene.[5] The same fulvene is also obtained from the condensation of cyclopentadiene with diethoxy(dimethylamino)methane.[6]

4. Merits of the Preparation

This procedure illustrates formylation by N,N-dimethylaminomethoxymethylium methyl sulfate, a compound which can be produced readily by reaction of easily available materials. 6-(Dimethylamino)fulvene is a useful intermediate for the synthesis of various fused-ring nonbenzenoid aromatic compounds.

1. Institute for Organic Chemistry, University of Munich, Munich, Germany.
2. K. Hafner and H. Kaiser, *Org. Syntheses*, **44**, 94 (1964).
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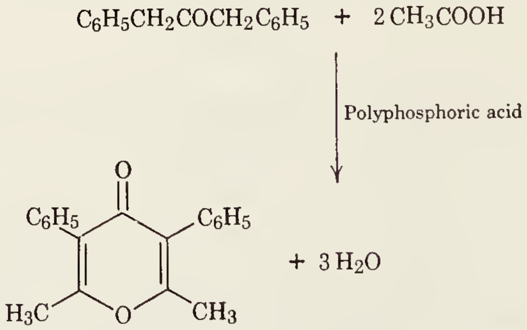
6. H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Ann.*, **641**, 1 (1961).

2,6-DIMETHYL-3,5-DIPHENYL-4*H*-PYRAN-4-ONE

(4*H*-Pyran-4-one, 2,6-dimethyl-3,5-diphenyl-)



Submitted by Thomas L. Emmick and Robert L. Letsinger[1]
Checked by Donald J. MacGregor and Peter Yates

1. Procedure

A mixture of 400 g. of polyphosphoric acid and 250 ml. of glacial acetic acid is heated to reflux in a 2-l. round-bottomed flask equipped with a stirrer, reflux condenser, and thermometer. Dibenzyl ketone (42.0 g., 0.200 mole) (Note 1) is then added, and the reaction mixture is heated at reflux (130–135°) for 1.5 hours. The solution is cooled to 30° in an ice water bath, and 1 l. of water is added slowly with stirring. The brown precipitate which forms is collected by filtration, washed with 1 l. of water, and dissolved in 1 l. of hot benzene. The hot benzene solution is treated with 2 g. of activated carbon, filtered hot through a pad of diatomaceous earth, dried with 10 g. of magnesium sulfate, decanted from the magnesium sulfate, and concentrated to 500 ml. On addition of 450 ml. of hexane and cooling to 5–10°, tan crystals of the crude pyranone separate. Filtration affords 25–27 g. (45–49%) of product melting at 202–206°. For purification this material is dissolved in 500 ml. of hot benzene, treated with 1 g. of activated carbon as before, and precipitated from solution by the addition of 250 ml. of hexane and cooling of the mixture to 5–10°. On filtration 19–21 g. (34–38%) of 2,6-dimethyl-3,5-diphenyl-4*H*-pyran-4-one is obtained. This material melts sharply at 207–209° (Note 2). An additional quantity (3–4 g., 5–7%) of somewhat less pure product (m.p. 204–206°) may be recovered by evaporation of the filtrate and recrystallization of the residue from 200 ml. of benzene-hexane (50% benzene by volume).

2. Notes

1. For this preparation Matheson, Coleman and Bell practical grade dibenzyl ketone was recrystallized once from anhydrous ether at −70°. It melted at 33–34°. Practical grade dibenzyl ketone may be used directly; however, the yield of the pyranone is somewhat lower.

2. The corrected melting point is 209.5–210.0°. Melting points were obtained with a Fisher-Johns apparatus. The recrystallized sample retained a pale tan shade.

3. Methods of Preparation

This procedure is a modification of that of Letsinger and Jamison.[2] The pyranone has also been prepared by treatment of dibenzyl ketone with acetic anhydride-perchloric acid or acetyl chloride-aluminum chloride.[3]

4. Merits of the Preparation

This procedure represents a simple and unique route to certain pyran-4-ones. The reaction can be applied also to benzyl methyl ketone and diethyl ketone; the corresponding pyran-4-ones are obtained in yields of 48% and 26%, respectively.

1. Northwestern University, Evanston, Illinois.
2. R. L. Letsinger and J. D. Jamison, *J. Am. Chem. Soc.*, **83**, 193 (1961).
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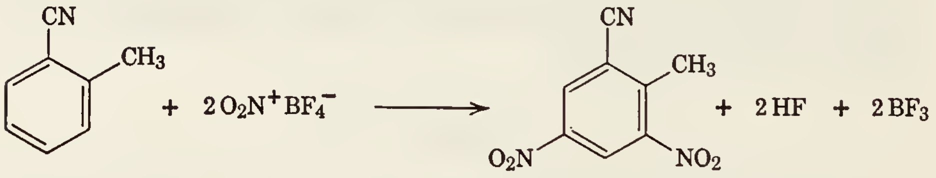
3,5-DINITRO-*o*-TOLUNITRILE

(Benzonitrile, 2-methyl-3,5-dinitro-)

$$HNO_3 + HF + 2BF_3 \longrightarrow O_2N^+BF_4^- + H_2O \cdot BF_3$$



Submitted by George A. Olah [1] and Stephen J. Kuhn [2]
Checked by J. Lazar and B. C. McKusick

1. Procedure

A. *Nitronium tetrafluoroborate* (*Note 1*). *Caution! Hydrogen fluoride is very hazardous. Caution is also called for in the use of boron trifluoride. All operations must be carried out in a hood, and the precautions outlined in Note 2 should be followed.* A 1-l. three-necked polyolefin flask (Note 3) is provided with a short inlet tube for nitrogen, a long inlet tube for gaseous boron trifluoride, a drying tube, and a magnetic stirring bar (Note 4). The flask is immersed in an ice-salt bath and flushed with dry nitrogen.

Under a gentle stream of nitrogen and with stirring, the flask is charged with 400 ml. of methylene chloride, 41 ml. (65.5 g., 1.00 mole) of red fuming nitric acid (95%), and 22 ml. (22 g., 1.10 moles) of cold, liquid, anhydrous hydrogen fluoride (Note 5).

Gaseous boron trifluoride (136 g., 2.00 moles) from a cylinder mounted on a scale is bubbled into the stirred, cooled reaction mixture (Note 6). The first mole is passed in rather quickly (in about 10 minutes). When approximately 1 mole has been absorbed, copious white fumes begin to appear at the exit, and the rate of flow is diminished so that it takes about 1 hour to pass in the second mole; even at this slow rate, there is considerable fuming at the exit. After all the boron trifluoride has been introduced, the mixture is allowed to stand in the cooling bath under a slow stream of nitrogen for 1.5 hours. The mixture is swirled, and the suspended product is separated from the supernatant liquid by means of a medium-porosity, sintered-glass Buchner funnel (Note 7). The gooey solid remaining in the flask is transferred to the funnel with the aid of two 50-ml. portions of nitromethane. The solid on the funnel, nitronium tetrafluoroborate, is washed successively with two 100-ml. portions of nitromethane and two 100-ml. portions of methylene chloride. In order to protect the salt from atmospheric moisture during the washing procedure, suction is always stopped while the salt is still moist. The moist salt is transferred to a round-bottomed flask and dried by evaporating the solvent (Note 8). At the end of the procedure the flask can be gently heated to 40–50° (Note 9). The yield of colorless nitronium tetrafluoroborate is 85–106 g. (64–80%) (Notes 10, 11, 12). It is stored in a wide-mouthed polyolefin bottle with a screw cap. The edge of the cap is sealed with paraffin wax after it is screwed on.

B. *3,5-Dinitro-o-tolunitrile.* A 500-ml. four-necked flask is equipped with a mechanical stirrer, a dropping funnel, a thermometer, and an inlet for dry nitrogen (Note 13). It is baked thoroughly by means of a Bunsen flame and allowed to cool to room temperature with a slow stream of dry nitrogen passing through it. The flask is charged, preferably in a dry box, with 335 g. of tetramethylene sulfone (Note 14) and 73.1 g. (0.55 mole) of nitronium tetrafluoroborate. The thermometer is adjusted so that the bulb is immersed in the liquid. The reaction mixture is stirred well and kept at 10–20° by means of an ice bath while 58.5 g. (0.50 mole) of freshly distilled *o*-tolunitrile[3] is added dropwise. The nitronium tetrafluoroborate only partially dissolves in the tetramethylene sulfone (Note 15), but through good stirring a homogeneous suspension can be obtained. As the dissolved nitronium salt reacts with the nitrile, more and more salt dissolves until all of it is in solution. The addition of *o*-tolunitrile requires 25–35 minutes.

After the addition is complete, the cooling bath is removed and stirring is continued for 15 minutes at 35°. The dropping funnel is removed, 74.5 g. (0.56 mole) of nitronium tetrafluoroborate is added, and the opening of the flask is closed with a glass stopper. The well-stirred reaction mixture is heated by an electric heating mantle to 100° in 15 minutes and kept at 100–115° for 1 hour. The reaction mixture is allowed to cool to room temperature with continued stirring and is then poured into 800 g. of ice water. Crude 3,5-dinitro-*o*-tolunitrile separates on top of the aqueous mixture as a dark oil that solidifies after standing a few minutes. The solid is collected on a Buchner funnel. It is triturated on the funnel with five 50-ml. portions of cold water and with 40 ml. of ice-cold ethanol. After being dried in a vacuum desiccator, the crude nitrile weighs 75–84 g., m.p. 60–65°. Recrystallization from about 110 ml. of hot methanol gives 50–55 g. (48–53%) of 3,5-dinitro-*o*-tolunitrile, m.p. 82–84° (Note 16).

2. Notes

1. Nitronium tetrafluoroborate is commercially available from the Ozark-Mahoning Co., Tulsa, Oklahoma.

2. *Because of the hazardous nature of anhydrous hydrogen fluoride, adequate precautions should be taken to protect the head, eyes, and skin.* Rubber gloves, an apron, and a plastic face mask are strongly recommended. All operations should be carried out in a hood. If hydrogen fluoride comes in contact with the skin, the contacted area should be thoroughly washed with water and then immersed in ice water while the patient is taken to a physi-

cian. After completion of the reaction, all equipment should be washed with liberal quantities of water. *Note! Burns caused by hydrogen fluoride may not be noticed for several hours, by which time serious tissue damage may have occurred.*

3. All operations involving liquid hydrogen fluoride must be carried out with equipment resisting hydrogen fluoride (fused silica, polyolefin, etc.).

4. An egg-shaped stirrer seems to work best. As the reaction proceeds, the precipitating nitronium tetrafluoroborate prevents the stirring bar from operating. This is not serious if the reaction mixture is shaken occasionally.

5. It is convenient to condense anhydrous hydrogen fluoride, b.p. 19.5°, from a cylinder into a small calibrated polyolefin flask immersed in a mixture of dry ice and acetone. As hydrogen fluoride is very hygroscopic, it should be carefully protected from atmospheric moisture, preferably by maintaining an atmosphere of dry nitrogen over it, otherwise by means of a drying tube. The hydrogen fluoride is then simply poured into the reaction flask.

6. The temperature of the reaction is not critical, but the reaction is slower at higher temperatures because of the lower solubility of boron trifluoride in the solvent.

7. Since free hydrogen fluoride is no longer present, filtration can be carried out with glass or porcelain equipment. However, commercially available polyolefin Buchner funnels and filter flasks are preferred.

8. Kel-F grease is recommended for ground-glass joints. Nitronium tetrafluoroborate slowly attacks silicone stopcock grease, causing air to enter the flask.

9. Nitronium tetrafluoroborate is thermally stable up to 170°. Above this temperature it starts to dissociate into nitryl fluoride and boron trifluoride.

10. Nitronium tetrafluoroborate is very hygroscopic. It is stable as long as it is anhydrous, but it is decomposed by moisture, and all transfers should be in a dry box. Its purity can be checked by conventional elemental analysis. However, because of the hygroscopic nature of the salt, the submitters have found it convenient to use neutron activation analysis (B, F, N, O) of samples

sealed into polyolefin sample holders. Lange's method[4] for the determination of BF_4^- as the nitron salt gives good results but requires considerable care to achieve reproducibility.

11. The last part of the procedure can be used to purify nitronium tetrafluoroborate that has picked up water on standing. The impure salt is washed twice with nitromethane, twice with methylene chloride, and is dried under reduced pressure.

12. Nitronium tetrafluoroborate slowly attacks polyethylene and polypropylene, but apparatus made of these materials will last for several preparations of the salt.

13. The entire operation should be carried out in an atmosphere of dry nitrogen. If dry nitrogen is not available, rigorously anhydrous conditions should be maintained with the help of a drying tube.

14. Tetramethylene sulfone is commercially available from the Shell Chemical Company and the Phillips Petroleum Company.

15. A saturated solution at 25° contains 7 g. of nitronium tetrafluoroborate per 100 g. of tetramethylene sulfone.

16. This is pure enough for most purposes. An analytical sample melted at 86.5–88.4°.

3. Methods of Preparation

Nitronium tetrafluoroborate has been prepared by interaction of nitric acid, hydrogen fluoride, and boron fluoride in nitromethane.[5] However, mixtures of nitric acid and nitromethane are extremely explosive.[6, 7] The present modification of the procedure, in which the medium is methylene chloride instead of nitromethane, was developed to avoid this hazard. It has not been published before.

The preparation of 3,5-dinitro-*o*-tolunitrile is based on previously published work.[8] The nitration of *o*-tolunitrile using fuming nitric acid has been reported by Candea and Macovski.[9]

4. Merits of the Preparation

Nitration of aromatic rings by nitronium tetrafluoroborate is a general method. Fifty-seven arenes, haloarenes, nitroarenes, arenecarboxylic esters, arenecarbonyl halides, and arenecarbonitriles have been nitrated in high yield by this reagent.[8] The method is particularly convenient for nitrating aromatic compounds susceptible to acid-catalyzed hydrolysis. For example, although mononitration of arenecarbonitriles is easily accomplished by conventional nitrating agents, dinitration is not. The reason is that the forcing conditions required for dinitration (strongly acid media and higher temperatures) bring about hydrolysis (and oxidation) of the nitrile group. In contrast, nitrations with nitronium tetrafluoroborate can be carried out in nonaqueous acid-free systems, where the only acid originates from proton elimination during nitration. In the basic solvent used, this acid concentration generally is not sufficient to cause any detectable hydrolysis (or oxidation).

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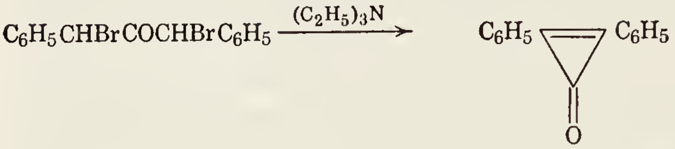
DIPHENYLCYCLOPROPENONE

$$C_6H_5CH_2COCH_2C_6H_5 + 2Br_2 \longrightarrow C_6H_5CHBrCOCHBrC_6H_5 + 2HBr$$



Submitted by R. Breslow and J. Posner[1]
Checked by E. J. Corey and M. F. Semmelhack

1. Procedure

A. *α,α′-Dibromodibenzyl ketone.* To a solution of 70 g. (0.33 mole) of commercial dibenzyl ketone in 250 ml. of glacial acetic acid in a 2-l. one-necked flask fitted with a magnetic stirrer a solution of 110 g. (0.67 mole) of bromine in 500 ml. of acetic acid is added through a dropping funnel over a 15-minute period. After addition is complete, the mixture is stirred for an additional 5 minutes and is then poured into 1 l. of water. Solid sodium sulfite is added in small portions until the initial yellow color of the solution is discharged, and the mixture is allowed to stand for 1 hour. The slightly yellow dibromoketone is then collected by filtration and air-dried. Recrystallization from 1 l. of ligroin yields 97 g. of white needles, m.p. 79–87°; an additional 11 g., m.p. 79–83°, is obtained by concentrating the mother liquors, and the two crops are combined (Note 1).

B. *Diphenylcyclopropenone.* A solution of 100 ml. of triethylamine (Note 2) in 250 ml. of methylene chloride is magnetically stirred in a 2-l. one-necked flask while 108 g. (0.29 mole) of the above dibromoketone in 500 ml. of methylene chloride is added dropwise over 1 hour. The mixture is stirred for an additional 30 minutes and then extracted with two 150-ml. portions of 3N hydrochloric acid; the aqueous extracts are discarded. The red organic solution is transferred to a 2-l. Erlenmeyer flask and cooled in an ice bath. While this solution is swirled, a cold solution of 50 ml. of concentrated sulfuric acid in 25 ml. of water is slowly added. A slightly pink precipitate of diphenylcyclopropenone bisulfate gradually separates (Note 3). This is collected on a sintered-glass funnel and washed with two 100-ml. portions of methylene chloride. The solid is then returned to the flask (Note 4) along with 250 ml. of methylene chloride and 500 ml. of water, and 5 g. of solid sodium carbonate is added in small portions. The organic layer is collected and the aqueous solution extracted with two 150-ml. portions of methylene chloride. The combined organic layers are dried over magnesium sulfate and evaporated to dryness. The impure diphenylcyclopropenone is recrystallized by repeated extraction with boiling cyclohexane (total 1.5 l.), the solution being decanted in each case from a reddish oily impurity. On cooling, the solution deposits 29 g. of white crystals, and an additional 1 g. can be obtained by concentrating the mother liquors to 150 ml. The combined 30 g., m.p. 119–120°, represents an overall yield of 44% based on dibenzylketone.

2. Notes

1. Care should be taken to prevent either the dibromoketone or the cyclopropenone from coming into contact with the skin, as allergic reactions have been observed in several cases. The use of gloves is recommended especially for the bromoketone. The latter product has a wide melting range because it is a mixture of the *meso*- and *d,l*-compounds.

2. For best results the commercial triethylamine (Matheson, b.p. 89–90°) should be purified to remove primary and secondary amines and water, either by distillation from acetic anhydride and then from barium oxide, or by reaction with phenylisocyanate.[2, 3]

3. If the white solid fails to separate after 15–30 minutes, concentrated sulfuric acid is added in 4-ml. portions to the cooled solution with swirling until the white solid appears.

4. Since some of the white solid adheres to the walls of the flask, it is convenient to use the same flask for the neutralization after rinsing it with methylene chloride.

3. Methods of Preparation

Diphenylcyclopropenone has also been prepared by the action of phenylchlorocarbene on phenylketene acetal[4] and by the reaction of dihalocarbene with diphenylacetylene.[5] The present procedure[6] is the most convenient on a preparative scale.

4. Merits of the Preparation

Diphenylcyclopropenone is the first stable molecule prepared which has a carbonyl group in a three-membered ring. In a very real sense the compound has aromatic character and is fairly stable.[4] An interesting cycloaddition reaction of enamines with diphenylcyclopropenone has been reported.[7]

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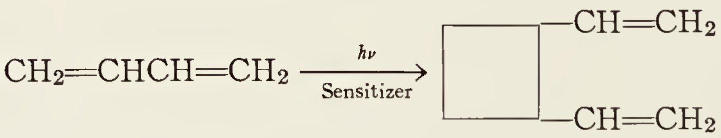
cis- AND *trans*-1,2-DIVINYLCYCLOBUTANE



Submitted by Charles D. DeBoer,[1] Nicholas J. Turro,[2]
and George S. Hammond[1]
Checked by William G. Dauben and James H. Smith

1. Procedure

Caution! This reaction should be carried out in an explosion-proof room behind a safety shield because it involves a glass vessel under pressure.

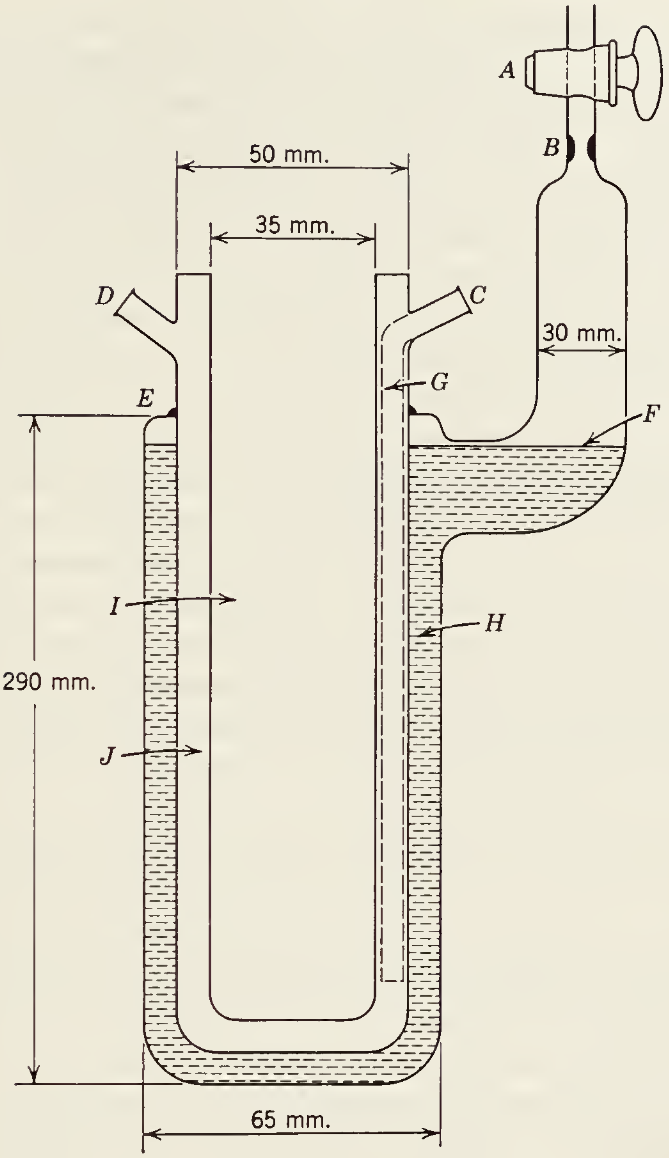


FIG. 1. *A*, 4-mm. stopcock; *B*, thickened for easy sealing; *C*, water inlet; *D*, water outlet; *E*, this seal can be replaced by a ground glass joint for higher-boiling materials than butadiene; *F*, filling level; *G*, the cooling water tube indicated by the dotted lines will permit a higher flow rate if shaped as an oval or rectangle; *H*, reaction well; *I*, lamp well; *J*, cooling water jacket.

A reaction vessel as shown in Fig. 1 is made from Pyrex tubing (Note 1). The vessel is evacuated and the stopcock closed. A 500-ml. round-bottomed, two-necked flask equipped with a gas inlet and a cold finger condenser containing dry ice is charged with 1 g. of *finely powdered* 4,4′-bis(dimethylamino)benzophenone

(Michler's ketone) (Notes 2, 3). A butadiene tank is connected to the gas inlet, and about 250 ml. (160 g., 3.0 moles) of butadiene is collected in the flask (Note 4). The butadiene is cooled to dry ice temperature. The reaction vessel is immersed to the filling level shown in Fig. 1 in a slurry of dry ice and acetone. A 4-in. length of Tygon tubing is attached between the inlet of the reaction vessel and one neck of the flask containing the butadiene. The other neck of the flask is stoppered, and the flask is tipped to fill the connecting tube and the neck of the stopcock with butadiene. At the same time the stopcock is opened. The flask is shaken to ensure that the suspended Michler's ketone will be swept into the reaction vessel by the butadiene. After the vessel is filled with butadiene the stopcock is closed, the connecting tube removed, and the vessel transferred to a Dewar flask filled with liquid nitrogen. When the butadiene is frozen, the vessel is evacuated with a high-vacuum pump and sealed off below the stopcock with a torch (Note 5). The reaction vessel is fitted with cooling water hoses and a 450-watt Hanovia medium-pressure mercury arc lamp, and then the butadiene is allowed to thaw and come to room temperature (Note 6). The mixture is irradiated for 72 hours, the water jacket dried, and the vessel weighed (*Caution!* Note 6). The reaction vessel is then frozen in a Dewar flask containing a dry ice-acetone mixture, and the seal is cautiously broken. The cooling bath is removed, and the reactor is allowed to come to room temperature. The reaction mixture is removed, the vessel cleaned (Note 7), and weighed again to determine the amount of starting material. The reaction mixture is distilled and the fraction boiling between 109° and 111° (uncor.) is collected (Note 8). The yield is 96–104 g. (60–65%) of 99% pure (by gas chromatography) *trans*-1,2-divinylcyclobutane, $n^{25}\text{D}$ 1.4429–1.4431, the impurities being butadiene and 1,5-cyclooctadiene (Note 9).

2. Notes

1. A reaction vessel, as shown in Fig. 1, is useful for many photochemical reactions because virtually all the light produced can be captured by the reagents. It can be constructed from

either Pyrex or quartz tubing, depending on the absorption spectra of the reagents.

2. The choice of a sensitizer for butadiene dimerization depends on three things: the energy of the triplet-singlet transition, the intersystem crossing efficiency, and the absorption spectrum of the sensitizer.[3] Michler's ketone has a sufficiently high triplet energy to transfer energy at a diffusion-controlled rate to both *cis* and *trans* forms of butadiene, thus reducing the yield of 4-vinylcyclohexene produced.[4] Furthermore it has a high intersystem crossing efficiency and a high extinction coefficient at 3660 Å, which is the most intense line from a medium-pressure mercury arc lamp. For photochemical reactions where energy transfer is not diffusion-controlled, the lifetime of the triplet may be an important factor in the choice.

3. The amount of sensitizer is not critical since only enough is needed to absorb all the light. One gram of Michler's ketone will not be totally dissolved in 250 ml. of butadiene, but will be totally dissolved after the reaction is finished. Michler's ketone as obtained from Eastman Organic Chemicals was used without purification.

4. 1,3-Butadiene obtained from Matheson, Coleman and Bell was used without purification.

5. The butadiene should not be degassed by freeze-thaw cycles, because the presence of a small amount of oxygen reduces the amount of polymer formed on the walls of the vessel.

6. All experimental manipulations with the reaction vessel while it is sealed and under pressure should be carried out behind a safety shield.

7. The polymer can be conveniently removed by filling the flask two-thirds full with concentrated nitric acid and warming gently on a steam bath in a hood behind a safety shield.

8. The *cis*-1,2-divinylcyclobutane in the reaction mixture rearranges rapidly under reflux to the higher-boiling 1,5-cyclooctadiene.

9. If *cis*-1,2-divinylcyclobutane is desired, it can be isolated in 7–8% yield from the reaction mixture by preparative gas chromatography with the Beckman Megachrom instrument, using columns packed with Apiezon J.

3. Methods of Preparation

The *trans* isomer of 1,2-divinylcyclobutane may be isolated in low yield from the mixture formed by thermal dimerization of butadiene.[5] The *cis* isomer has been prepared by a sequence of reactions.[6]

4. Merits of the Preparation

Essentially the same procedure may be used to produce mixtures of cyclodimers from isoprene,[4] 1,3-cyclopentadiene,[4] and 1,3-cyclohexadiene.[7] Separation of all products is somewhat difficult in most cases but has always been possible by preparative vapor phase chromatography. Despite the problems that may be involved in separation of desired products in some instances, photocyclization frequently is the method of choice for preparation of 1,2-dialkenylcyclobutanes if they can be made major products of photoreactions. Starting materials are readily available, and the preparations are easily carried out on the scale described. There is little doubt that the method is the best for preparation of *trans*-1,2-divinylcyclobutane.

1. Contribution No. 3131 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.
2. Department of Chemistry, Columbia University, New York, New York.
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5. E. Vogel, *Ann.*, **615**, 1 (1958).
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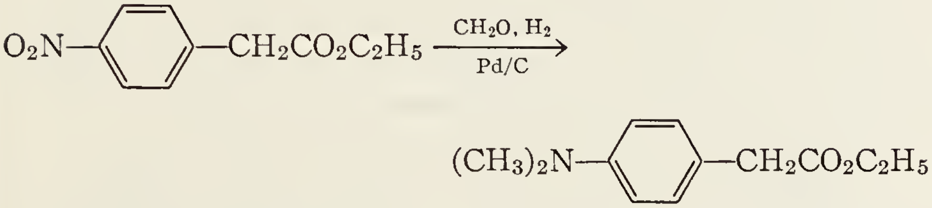
ETHYL *p*-DIMETHYLAMINOPHENYLACETATE

(Acetic acid, *p*-dimethylaminophenyl-, ethyl ester)



Submitted by Michael G. Romanelli and Ernest I. Becker [1]
Checked by Roy A. Sikstrom, Douglas R. Johnson,
William E. Parham, and Wayland E. Noland

1. Procedure

In a 400-ml. Parr bottle are placed 41.8 g. (0.20 mole) of ethyl *p*-nitrophenylacetate, 40 ml. of 40% aqueous formaldehyde solution, 200 ml. of 95% ethanol, and 2.0 g. of 10% palladium on charcoal (Note 1). The bottle is then placed on a Parr hydrogenation apparatus. The sample is evacuated and filled with hydrogen, this process being repeated three times. The tank and bottle are then filled with hydrogen to 55 p.s.i. The shaker is started, and the hydrogenation is allowed to proceed until the pressure drop corresponds to 1.0 mole of hydrogen (Notes 2, 3). The time required for hydrogenation is approximately 2.5 hours (Note 4). After venting the hydrogen from the bottle safely (Note 1), the ethanol solution is filtered and the catalyst washed carefully (Note 5) with 20 ml. of ethanol.

The filtrate is transferred to a flask which is placed on a rotary evaporator. The ethanol is then removed under reduced pressure on a steam bath. Using ether as a washing solvent, the residue is transferred to a small distilling flask and the ether distilled. The ethyl *p*-dimethylaminophenylacetate is then distilled (Notes 6, 7) at reduced pressure, affording 27.7–31.8 g. (67–77%) of colorless product, b.p. 122–124° (0.4 mm.), $n^{23}\text{D}$ 1.5358.

2. Notes

1. Care must be taken in weighing out and transferring the catalyst as it can ignite mixtures of air and flammable vapors. The operation of the Parr apparatus and appropriate safety precautions in its use have been described in detail.[2]

2. The hydrogenation is exothermic, and care must be taken in order to prevent the reaction from getting out of control. The submitters have not experienced this difficulty, but exothermic hydrogenations require supervision.

3. With the apparatus used, a pressure drop of 85 lb. corresponds to 1.0 mole of hydrogen. Either the particular apparatus used can be calibrated or the hydrogenation allowed to proceed until the pressure ceases to drop.[2]

4. The time required for the hydrogenation will depend on several factors, such as the speed of shaking, activity and particle size of the catalyst. In the experiments run on ethyl *p*-nitrophenylacetate the submitters have found that the time required varied from about 2 to 4 hours.

5. The filtration was by suction. The catalyst must not be allowed to dry out with a stream of air passing through it, as it can then readily ignite.

6. Before the actual distillation could be carried out, the flask was heated to approximately 95° and the residual formaldehyde removed at the aspirator. Only after the formaldehyde was removed could the pressure be reduced to that required for the distillation.

7. The checkers observed that rather rapid decomposition of the product occurs unless precautions were taken. A short path distillation using a 50-ml. distilling flask equipped with a capillary nitrogen bubbler was employed.

3. Methods of Preparation

Ethyl *p*-dimethylaminophenylacetate has been previously prepared in this laboratory by Fischer esterification of *p*-dimethylaminophenylacetic acid, the acid in turn being prepared by the reductive hydrolysis of *p*-dimethylaminomandelonitrile.[3]

4. Merits of the Preparation

Besides being a convenient preparation for ethyl *p*-dimethylaminophenylacetate, the procedure for reductive alkylation can be generalized.[4, 5] Table I lists the results obtained by the submitters.

TABLE I

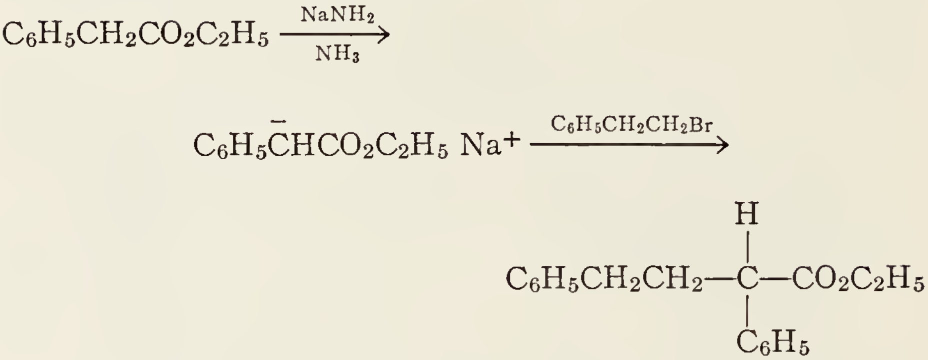
Reductive Alkylation of Nitro Compounds

Nitro Compound	% Yield
p-Nitrophenylacetic acid	84–91
p-Nitrobenzoic acid	87
m-Nitrobenzoic acid	95
p-Nitrotoluene	90
o-Nitrotoluene	76

1. Department of Chemistry, University of Massachusetts, Boston, Massachusetts. This work was carried out at the Polytechnic Institute of Brooklyn, Brooklyn, New York.
2. R. Adams and V. Voorhees, *Org. Syntheses*, Coll. Vol. **1**, 61 (1941).
3. Celal Tüzün and E. I. Becker, unpublished results.
4. R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, 1342 (1950).
5. W. S. Emerson, *Org. Reactions*, **4**, 174 (1948).

ETHYL 2,4-DIPHENYLBUTANOATE

(Butyric acid, 2,4-diphenyl-, ethyl ester)



$$C_6H_5CH_2CO_2C_2H_5 \xrightarrow[NH_3]{NaNH_2} C_6H_5\overset{-}{C}HCO_2C_2H_5\ Na^+ \xrightarrow{C_6H_5CH_2CH_2Br} C_6H_5CH_2CH_2{-}\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}{-}CO_2C_2H_5$$

Submitted by Edwin M. Kaiser, William G. Kenyon, and Charles R. Hauser[1]
Checked by Joseph G. Pfeiffer and Kenneth B. Wiberg

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide[2] (0.1 mole) in liquid ammonia is prepared in a 500-ml. three-necked, round-bottomed flask fitted with a West condenser, a ball and socket glass mechanical stirrer (Note 1), and a dropping funnel. In the preparation of this reagent a small piece of clean sodium metal is added to 350 ml. of commercial anhydrous liquid ammonia. After the appearance of a blue color, a few crystals of hydrated ferric nitrate are added, whereupon the blue color is discharged. The remainder of the 2.3 g. (0.1 mole) of sodium (Note 2) is then rapidly added as small pieces. After all the sodium has been converted to sodium amide (Note 3), a solution of 16.4 g. (0.1 mole) of ethyl phenylacetate (Note 4) in 35 ml. of anhydrous ethyl ether is added dropwise over a 2-minute period, and the mixture is stirred for 20 minutes. To the dark green suspension is added over an 8-minute period a solution of 18.5 g. (0.1 mole) of (2-bromoethyl)benzene (Note 4) dissolved in 35 ml. of anhydrous ethyl ether. The mixture is stirred for 3 hours and is then neutralized by the addition of 5.35 g. (0.1 mole) of ammonium chloride. After addition of 150 ml. of dry ethyl ether, the ammonia is evaporated with stirring by use of a warm water bath (Note 5). The mixture is then cooled to 0° by an ice bath and hydrolyzed by the dropwise addition of 100 ml. of 3*N* hydrochloric acid. After stirring for 15 minutes, the mixture is allowed to warm to room temperature, and the layers are separated. The aqueous layer is extracted with two 50-ml. portions of ethyl ether. The combined ether extracts are then washed with two 50-ml. portions of saturated aqueous sodium bicarbonate followed by two 50-ml. portions of saturated sodium chloride. Drying is accomplished over magnesium sulfate. After filtration and solvent removal, the crude product is purified by vacuum distillation to give 20.6–21.8 g. (77–81%) of ethyl 2,4-diphenylbutanoate, b.p. 168–169° (3.5 mm.). Vapor phase chromatography shows the presence of one peak (Note 6).

2. Notes

1. Stirrers with Teflon paddles should not be used.
2. The sodium was weighed in toluene and then rinsed in anhydrous ethyl ether.
3. Conversion is indicated by the discharge of the blue color.
4. Ethyl phenylacetate and (2-bromoethyl)benzene as supplied by Eastman Organic Chemicals were used without further purification.
5. Alternatively, the ammonia may be evaporated after the ammonium chloride and ethyl ether have been added by allowing the flask to stand overnight with stirring.
6. A 5-ft. Apiezon L column at 225° was used.

3. Methods of Preparation

The procedure described is a modification of that given by Kenyon, Meyer, and Hauser.[3] No other methods appear to have been used to prepare ethyl 2,4-diphenylbutanoate. A number of alkylations of ethyl phenylacetate have previously been effected with alkyl halides by means of other basic reagents, but the yields generally have not been very satisfactory.[4, 5]

4. Merits of the Preparation

The method described is successfully used for the alkylation and aralkylation of ethyl and *t*-butyl phenylacetate.[3] The alkylation of ethyl phenylacetate with methyl iodide, *n*-butyl bromide, benzyl chloride, and α-phenylethyl chloride affords the corresponding pure monoalkylation products in 69%, 91%, 85%, and 70% (*erythro* isomer) yields, respectively. The alkylation of *t*-butyl phenylacetate with methyl iodide, *n*-butyl bromide, α-phenylethyl chloride, and β-phenylethyl bromide gives the corresponding pure monoalkylated products in 83%, 86%, 72–73%, and 76% yields, respectively.

Certain of the monoalkylated ethyl phenylacetates have been further alkylated with alkyl and aralkyl halides to produce the corresponding disubstituted phenylacetic esters.[6] Ethyl 2-phenylpropanoate has been alkylated by methyl iodide to give pure ethyl 2-methyl-2-phenylpropanoate in 81% yield. Similarly, the alkylations of ethyl 2-phenylhexanoate with methyl iodide, *n*-butyl bromide, and benzyl chloride gave the corresponding pure dialkylated products in 73%, 92%, and 72% yields, respectively.

Butylation of ethyl phenylacetate, *t*-butyl phenylacetate, and ethyl 2-phenylhexanoate has also been accomplished with *n*-butyl bromide and sodium hydride in refluxing monoglyme in 64%, 66%, and 56% yields, respectively.[6] In contrast to the sodium amide reactions above, however, careful fractionation of the crude products was required to obtain pure products.

1. Department of Chemistry, Duke University, Durham, North Carolina. This work was supported by the U. S. Army Research Office — Durham.
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6. W. G. Kenyon, E. M. Kaiser, and C. R. Hauser, *J. Org. Chem.*, **30**, 2937 (1965).

4-HEPTANONE

$$2\,CH_3CH_2CH_2COOH + Fe \longrightarrow (CH_3CH_2CH_2COO)_2Fe + H_2$$

$$(CH_3CH_2CH_2COO)_2Fe \xrightarrow{\Delta} (CH_3CH_2CH_2)_2CO + FeO + CO_2$$

Submitted by Robert Davis, Charles Granito, and Harry P. Schultz[1]
Checked by William G. Dauben and Richard J. Shavitz

1. Procedure

A mixture of 370 ml. (4 moles) of *n*-butyric acid (Note 1) and 123 g. (2.2 moles) of hydrogen-reduced iron powder (Note 2) is refluxed for 5 hours in a 1-l. flask equipped with a condenser (Note 3). The apparatus is converted for downward distillation while an atmosphere of nitrogen is maintained. The nitrogen sweep is then stopped, the flask is strongly heated, and the entire distillate collected.

The crude product is washed with two 20-ml. portions of 10% sodium hydroxide solution and with one 20-ml. portion of water. The 4-heptanone is dried over 5 g. of anhydrous sodium sulfate, filtered, and distilled. The yield of 4-heptanone, b.p. 142–144°, n^{25}_D 1.4031–1.4036, is 157–171 g. (69–75%).

2. Notes

1. *n*-Butyric acid, b.p. 162–164°, from Eastman Organic Chemicals was redistilled before use.

2. Hydrogen-reduced iron powder from Fisher Scientific Company was used.

3. Severe foaming may force brief cessations of heating during the first hour. Boric acid (0.1 g.) somewhat diminishes the extent of foaming.

3. Methods of Preparation

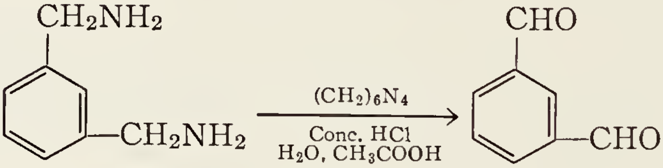
The present procedure is that of Davis and Schultz.[2] 4-Heptanone has also been synthesized by virtually every general method known and listed for ketones in "Chemistry of Carbon Compounds," including liquid or vapor phase decarboxylation of *n*-butyric acid or its salts, oxidation of 4-heptanol, and hydration of 3-heptyne.[3]

4. Merits of the Preparation

This method is illustrative of a general method of preparing simple ketones from normal aliphatic carboxylic acids. It is especially useful because the starting materials are easily accessible, the yields good, and the procedure very simple.

1. Chemistry Department, University of Miami, Coral Gables, Florida 33124.
2. R. Davis and H. P. Schultz, *J. Org. Chem.*, **27**, 854 (1962).
3. J. G. Buchanan, N. A. Hughes, F. J. McQuillin, and G. A. Swan in S. Coffey, "Rodd's Chemistry of Carbon Compounds," Elsevier Publishing Company, New York, New York, 1965, p. 53.

ISOPHTHALALDEHYDE



Submitted by J. H. Ackerman and A. R. Surrey[1]
Checked by Kenneth H. Brown, Wayland E. Noland,
and William E. Parham

1. Procedure

A solution of 272 g. (261 ml., 2.00 moles) of α,α'-diamino-*m*-xylene (Note 1), 1.00 kg. (7.1 moles) of hexamethylenetetramine, 480 ml. of concentrated hydrochloric acid, and 3.2 l. of 50% aqueous acetic acid in a 12-l. flask is stirred and heated at the reflux temperature for 2.5 hours. The hot amber reaction mixture is then poured into a large battery jar in a well-ventilated hood, and a solution prepared from 298 g. of sodium hydroxide and 3.85 l. of water is added slowly with stirring (Note 2). The mixture is covered and allowed to stand overnight at about 5°. The product, which separates as long needles, is collected, washed on a Buchner funnel with 100 ml. of cold water, and then dried to constant weight under vacuum (Note 3) over calcium chloride. There is obtained 158–166 g. (59–62%) of almost colorless needles of isophthalaldehyde, m.p. 88–90° (Note 4).

2. Notes

1. α,α'-Diamino-*m*-xylene was obtained from California Chemical Company and Aldrich Chemical Company.

2. The sodium hydroxide solution is added to neutralize most of the acetic acid present. Better yields are obtained using this neutralization procedure than by merely cooling the reaction mixture.

3. The checkers observed that house vacuum removed only 50% of the water after 48 hours.

4. One lot of α,α'-diamino-*m*-xylene from Aldrich Chemical Company gave the isophthalaldehyde as pale pink, long needles, m.p. 88–90°. When 12.0 g. of this material was recrystallized from 500 ml. of water, there was obtained 10.9 g. (91%) of pale cream, long needles, m.p. 89–91°.

3. Methods of Preparation

The procedure described is a modification of the general procedure of Angyal[2] for the preparation of aldehydes from benzylamines by the Sommelet reaction. Isophthalaldehyde has been prepared from *m*-xylene by preparation of the tetrachloro derivative and hydrolysis,[3] from isophthaloyl chloride by the Rosenmund reaction,[4] from α,α'-dibromo-*m*-xylene by the Sommelet reaction,[5] and from isophthaloyl chloride by reduction with lithium tri-*t*-butoxyaluminumhydride.[6]

4. Merits of the Preparation

Isophthalaldehyde is a valuable intermediate. Although the yields obtained by some of the other reported methods of preparation are better than the yield obtained here, the availability of starting material and the simplicity of reaction make this method attractive.

This appears to be the first reported case of the Sommelet reaction starting with a diamine.

1. Sterling-Winthrop Research Institute, Rensselaer, New York.
2. S. J. Angyal, *Org. Reactions*, 8, 197 (1954).
3. A. Colson and H. Gautier, *Bull. Soc. Chim. France*, **45**, 509 (1886).
4. K. W. Rosenmund, F. Zetzsche, and C. Flütsch, *Ber.*, **54**, 2888 (1921).
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KETENE DI(2-METHOXYETHYL) ACETAL

[Ketene bis(2-methoxyethyl) acetal]

$$2\,CH_3OCH_2CH_2ONa + H_2C{=}CCl_2 \longrightarrow H_2C{=}C(OCH_2CH_2OCH_3)_2 + 2\,NaCl$$

Submitted by William C. Kuryla and John E. Hyre [1]
Checked by Earl M. Levi and Peter Yates

1. Procedure

In a dry 1-l. five-necked flask equipped with a mechanical stirrer, a reflux condenser (Note 1), a thermometer, a nitrogen inlet, and a stoppered port (Note 2) are placed 152 g. (2.00 moles) of 2-methoxyethanol (Note 3) and 50 g. of xylene (Note 4). A constant dry nitrogen purge is maintained on the apparatus throughout the following operations (Note 5). Metallic sodium (46.0 g., 2.00 moles) is added in small chunks through the stoppered port to the stirred reaction mixture over a 2-hour period at a temperature of 130–150°. After all the sodium has reacted (Note 6), heating is discontinued, and 120 g. (1.24 moles) of vinylidene chloride (Note 7) is added dropwise to the stirred reaction mixture over a 20-minute period. During the addition of vinylidene chloride the reaction mixture becomes dark, and its temperature increases rapidly from an initial 140° to a maximum of 170–175°. It then decreases as addition continues, and concomitant precipitation of sodium chloride is noted. Stirring is continued for an additional 10 minutes after completion of the addition of vinylidene chloride. Anhydrous diethyl ether (100 ml.) is slowly added, serving both to reduce the viscosity and to cool the reaction mixture to about 60°. This mixture is then filtered through a medium-grade fritted-glass funnel, and the sodium chloride cake is washed with several 20-ml. portions of fresh ether (Note 8).

The ethereal filtrate and washings are distilled under reduced pressure (Note 9) with the use of a 6-in. Vigreux column, and pure ketene di(2-methoxyethyl) acetal (Note 10) is obtained; b.p. 81–84° (2.0 mm.), $n^{25}\text{D}$ 1.4411, yield 98–132 g. (56–75%). The infrared spectrum of the product shows a very strong C=C absorption band at 1640 cm.$^{-1}$.

2. Notes

1. A dry ice type of condenser has been found to be the most satisfactory because of the low boiling point (32°) of the vinylidene chloride. An efficient water-cooled condenser is satisfactory, however.

2. An addition funnel is fitted in this port after the sodium addition is complete.

3. 2-Methoxyethanol (methyl Cellosolve) from Union Carbide Corporation, Chemicals Division, was used.

4. Xylene (analytical reagent grade) from Mallinckrodt Chemical Works was distilled from sodium before use.

5. This is essential to avoid both the excessive oxidation of the reactants and the danger of a sodium-sparked fire.

6. Small amounts of metallic sodium, such as a few *very* small spheres floating in the reaction mass, are tolerable as long as dry nitrogen is being continuously passed through the reaction flask. A slow nitrogen purge is also maintained on the apparatus during the addition of the vinylidene chloride. The checkers found that appreciable amounts of sodium remained unconsumed after 3.5 hours; they added more 2-methoxyethanol (10–12 g.) to complete the reaction (significant loss of this reagent appeared to occur from the port during addition of the sodium).

7. Vinylidene chloride (inhibited grade) from Dow Chemical Company was used.

8. The sodium chloride cake is washed with as many 20-ml. portions of ether as are required to make the filtrate essentially colorless (usually four or five).

9. The diethyl ether is collected directly into traps cooled in dry ice-acetone.

10. The directions of McElvain and Kundiger[2] regarding the storage of ketene acetals should be followed. The submitters have found that storage at 0°, in a bottle which was previously washed with a hot concentrated caustic solution, is satisfactory.

3. Methods of Preparation

Ketene di(2-methoxyethyl) acetal has been obtained by the present method with the use of diethylene glycol dimethyl ether as solvent.[3] Other methods for the preparation of ketene acetals include the dehydrohalogenation of a halo acetal with potassium *t*-butoxide[2, 4] and the reaction of an α-bromo orthoester with metallic sodium.[5]

4. Merits of the Preparation

This synthetic process is applicable to the preparation of other ketene acetal derivatives of β-alkoxy alcohols. Examples include the ketene acetal derivatives of tetrahydrofurfuryl alcohol and 1-methoxy-2-propanol.[3] There are a number of advantages in its use, including a simple, time-saving procedure, readily available and inexpensive reagents, and good yields of ketene acetal obtained by a *one-step* method.

1. Union Carbide Corporation, Technical Center, Research and Development Department, South Charleston, West Virginia.
2. S. M. McElvain and D. Kundiger, *Org. Syntheses*, Coll. Vol. **3**, 506 (1955).
3. W. C. Kuryla and D. G. Leis, *J. Org. Chem.*, **29**, 2773 (1964).
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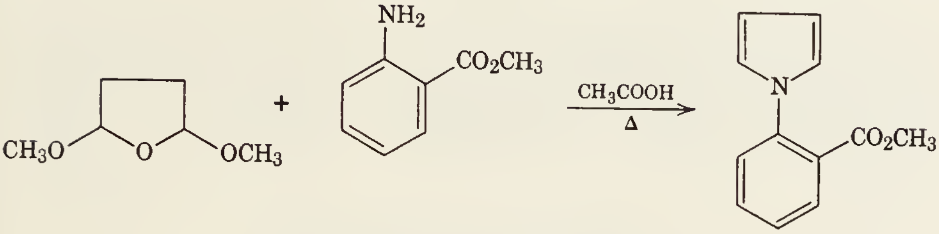
1-(2-METHOXYCARBONYLPHENYL)PYRROLE

[Pyrrole, 1-(2-methoxycarbonylphenyl)-]



Submitted by A. D. Josey[1]
Checked by William G. Dauben and Juraj Hostynek

1. Procedure

A solution of 90 g. (0.59 mole) of methyl anthranilate (Note 1) in 265 ml. of glacial acetic acid is placed in a 1-l. round-bottomed flask equipped with a reflux condenser and a magnetic stirrer. The stirrer is started, and 78 g. (0.59 mole) of 2,5-dimethoxytetrahydrofuran (Note 2) is added during 10–15 minutes (Note 3). The solution is heated under reflux for 1 hour, during which time the solution turns deep red to black in color. The heating is discontinued, the condenser is replaced with a Vigreux column, and the acetic acid is removed by distillation at aspirator pressure. The dark residue is distilled under reduced pressure through a 25-cm. column packed with glass helices, and 84–96 g. (70–80%) of slightly yellow 1-(2-methoxycarbonylphenyl)pyrrole is collected, b.p. 90–95° (2 mm.), n^{25}_{D} 1.5729.

2. Notes

1. Methyl anthranilate from Eastman Kodak Company was used without further purification.
2. 2,5-Dimethoxytetrahydrofuran from Eastman Kodak Company was used without further purification. This material also can be prepared by catalytic hydrogenation[2] of 2,5-dimethoxy-2,5-dihydrofuran.[3]

3. The submitter reports that much heat is liberated during the addition; the checkers did not find the reaction to be markedly exothermic.

3. Methods of Preparation

1-(2-Methoxycarbonylphenyl)pyrrole has not been prepared previously. An attempt to prepare the material via the mucic acid pyrrole synthesis using methyl anthranilate was unsuccessful.[4]

4. Merits of the Preparation

The condensation of primary amines with 2,5-dialkoxytetrahydrofurans to give in one step N-substituted pyrroles is applicable to a variety of substituted aliphatic and aromatic amines.[5] The method, largely developed by Clauson-Kaas and associates, has the advantages of simplicity, mild conditions, and generally excellent yields from readily available starting materials.

The submitter has used the method to prepare the corresponding 1-pyrrolyl derivatives[6] from the following amines in the indicated yields: ethyl β-aminobutyrate 88%, methyl β-aminoglutarate 87%, β-aminopropionitrile 58%, and 2,5-diamino-3,4-dicyanothiophene 22%.

On saponification 1-(2-methoxycarbonylphenyl)pyrrole yields 1-(2-carboxyphenyl)pyrrole, m.p. 106–107°, which on reaction with polyphosphoric acid at 70° is cyclized to 9-keto-9H-pyrrolo(1,2-*a*)indole in 28–32% yield. Through the choice of the appropriate amine and acetal components, the substituted 1-(2-methoxycarbonylphenyl)pyrroles become readily available intermediates in the preparation of a variety of derivatives of the pyrrolo(1,2-*a*)indole ring system.

1. Contribution No. 977 from the Central Research Department, Experimental Station, E.I. du Pont de Nemours and Co., Inc.
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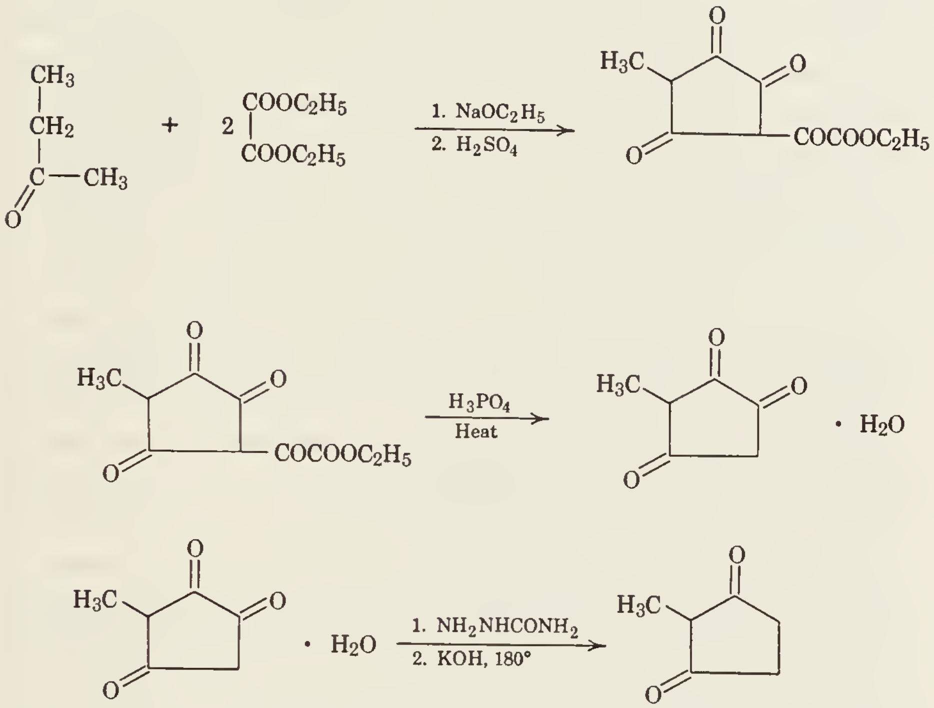
6. A. D. Josey and E. L. Jenner, *J. Org. Chem.*, **27**, 2466 (1962).

2-METHYLCYCLOPENTANE-1,3-DIONE

(1,3-Cyclopentanedione, 2-methyl-)



Submitted by Joseph P. John, S. Swaminathan,
and P. S. Venkataramani [1]
Checked by J. A. Berezowsky and Peter Yates

1. Procedure

A. *2-Methyl-4-ethoxalylcyclopentane-1,3,5-trione.* A solution of sodium ethoxide is prepared in a 2-l. three-necked, round-bottomed flask fitted with a mercury-sealed stirrer, a reflux condenser carrying a drying tube, and a stopper by the addition of 69.0 g. (3 moles) of sodium to 950 ml. of absolute ethanol. The solution is cooled to 0–5° in an ice bath and stirred. The stopper is replaced by a dropping funnel, and a cold mixture (5–15°) of 108 g. (1.50 moles) of freshly distilled 2-butanone and 482 g. (3.30 moles) of diethyl oxalate (Note 1) is added gradually over a period of 30 minutes. After the addition is complete, the thick, orange-red mixture is allowed to warm with continued stirring to room temperature, heated under reflux for 30 minutes, and cooled again to 0° in an ice bath. The mixture is decomposed by stirring with 165 ml. of sulfuric acid (1:1 by volume) added in portions. The sodium sulfate formed is filtered by suction and washed with ethanol (150–200 ml.) (Note 2). The washings and filtrate are combined and concentrated by evaporation at room temperature for 3–4 days in two wide-mouthed (6-in.) 1-l. crystallizing basins (Note 3). The yellowish brown product which accumulates by slow crystallization is collected by filtration, washed with small quantities of ice-cold water, and dried in air. The crude product weighs 140–150 g. Further evaporative concentration of the mother liquor followed by cooling furnishes an additional 40–50 g. of the keto ester, bringing the total yield to 180–200 g. (53–59%) (Note 2). This crude material (m.p. 120–130°) is used in the next step. A pure sample can be obtained by crystallization from ethyl acetate after treatment with Norit activated carbon, m.p. 160–162°.

B. *2-Methylcyclopentane-1,3,5-trione hydrate.* A mixture of 200 g. (0.89 mole) of the keto ester prepared above, 910 ml. of water, and 100 ml. of 85% phosphoric acid is heated under reflux for 4 hours and then cooled in an ice-salt bath to −5°. The trione mixed with oxalic acid separates and is collected by filtration and dried under reduced pressure. The dried material is extracted with boiling ether (250–300 ml.) under reflux, and the ethereal extract is separated from the undissolved oxalic acid. The original aqueous filtrate is also extracted with ether in a continuous extractor. The two extracts are combined, and ether is removed by distillation. The crude trione separates as a dark brown solid and is crystallized from *ca.* 250 ml. of hot water. The once-crystallized, faintly yellow product weighs 95–105 g. (74–82%), m.p. 70–74°. This product is used in the next step without further purification. A better specimen, m.p. 77–78°, which is almost colorless, can be obtained by recrystallization from hot water after treatment with Norit activated carbon.

C. *2-Methylcyclopentane-1,3,5-trione 5-semicarbazone.* The above trione hydrate (144 g., 1.00 mole) is dissolved in a mixture of 500 ml. of water and 1 l. of ethanol. A solution of 150 g. of sodium acetate in 200 ml. of water is added with stirring to raise the pH to 5–5.5, and the precipitate formed (Note 4) is filtered and washed with a little water (*ca.* 25 ml.). The filtrate is transferred to a 4-l. beaker and warmed to 45° on a water bath. Heating is then stopped, and a solution of 112 g. (1.00 mole) of semicarbazide hydrochloride and 150 g. of sodium acetate in 250 ml. of water is added dropwise from a dropping funnel with vigorous stirring during the course of 1.5 hours (Note 5). The stirring is continued for an additional hour, and the cream-colored monosemicarbazone is collected by filtration, washed with a little aqueous ethanol, and dried at 100°. The dried material weighs 110–120 g. (60–66%) and does not melt below 300°.

D. *2-Methylcyclopentane-1,3-dione.* In a 2-l. three-necked flask equipped with a reflux condenser and a stirrer are placed 115 g. (2.00 moles) of potassium hydroxide pellets and 1150 ml. of ethylene glycol. The flask is immersed in an oil bath which is heated to 130°. To the stirred mixture is added 12 ml. of water followed by 115 g. (0.628 mole) of the semicarbazone prepared above, added in portions over 30–40 minutes through the third neck of the flask, which is kept stoppered between additions. After the addition is complete, the bath temperature is raised to 150° and kept at this temperature for 30 minutes and then raised again to 180–185°. After 2 hours at 180–185° the reaction mixture is cooled, and the ethylene glycol is removed under reduced pressure (preferably below 4 mm.) (Note 6). The dry residue remaining is dissolved in 200–225 ml. of water, and the solution is cooled and carefully (Note 7) made acidic to Congo red with concentrated hydrochloric acid. The crude dione, which separates as a brown solid, is collected by filtration and crystallized from a mixture of 250 ml. of water and 200 ml. of ethanol after treatment with Norit activated carbon. The almost colorless crystalline product weighs 40–44 g., m.p. 206–207°. The mother liquor is concentrated to furnish an additional 10–12 g. of product, m.p. 204–205°. The crops are combined and recrystallized as before to give 42–47 g. (60–67%) of colorless dione, m.p. 211–212°.

2. Notes

1. Eastman Organic Chemicals or B.D.H. Laboratory reagent grade diethyl oxalate was used.

2. The checkers washed the sodium sulfate with 500 ml. of ethanol. They obtained 202–213 g. (60–63%) of product, m.p. 140–155°.

3. The combined filtrate and washings may be concentrated to about 350 ml. under reduced pressure with a bath temperature not exceeding 40° and then worked up as described. However, the final yield of the keto ester is decreased to 120–140 g.

4. This pale yellow precipitate weighs 20–30 g. and is rejected.

5. The conditions described for the preparation of the semicarbazone are critical and should be strictly observed. Otherwise, the yield of the product in the subsequent Wolff-Kishner reduction is decreased.

6. The checkers found that it is important to remove the ethylene glycol immediately upon completion of the reaction; in a run in which the reaction mixture was allowed to stand overnight, a drastic reduction in the yield of product was observed.

7. There is considerable evolution of carbon dioxide and consequent frothing during acidification. Care must be exercised so that the contents of the flask do not spill over.

3. Methods of Preparation

2-Methylcyclopentane-1,3-dione has been prepared in 15% yield by the catalytic reduction of 2-methylcyclopentane-1,3,5-trione over platinum.[2] The present method is based on the original procedure [3] of Panouse and Sannie with improvements as effected by Boyce and Whitehurst [4] and the submitters.[5]

4. Merits of the Preparation

2-Methylcyclopentane-1,3-dione has found increasing use as an intermediate in the synthesis of steroids.[6–12] The method described is the only practicable method available for the preparation of 2-methylcyclopentane-1,3-dione in large amounts.

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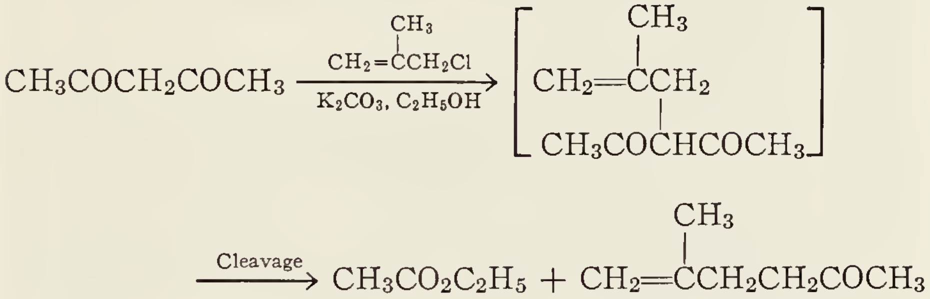
5-METHYL-5-HEXEN-2-ONE

(5-Methylene-2-hexanone)



$$CH_3COCH_2COCH_3 \xrightarrow[K_2CO_3,\ C_2H_5OH]{CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2Cl} \left[\begin{array}{c} CH_3 \\ | \\ CH_2{=}CCH_2 \\ | \\ CH_3COCHCOCH_3 \end{array}\right]$$

$$\xrightarrow{\text{Cleavage}} CH_3CO_2C_2H_5 + CH_2{=}\overset{CH_3}{\overset{|}{C}}CH_2CH_2COCH_3$$

Submitted by Sandra Boatman and Charles R. Hauser [1]
Checked by E. J. Corey and William E. Russey

1. Procedure

In a 1-l. round-bottomed flask equipped with a condenser are placed 78.0 g. (0.56 mole) of commercial anhydrous potassium carbonate, 45.0 g. (0.50 mole) of methallyl chloride (Note 1), 55.0 g. (0.55 mole) of 2,4-pentanedione (Note 1), and 300 ml. of anhydrous ethanol (Note 2). The mixture is refluxed on a steam bath for 16 hours. The condenser is replaced by a distilling head and condenser, and about 200 ml. of ethanol is distilled from the mixture (Note 3). Ice water (600 ml.) is added to dissolve the salts, and the mixture is extracted three times with ether. The combined ether extracts are washed twice with 100 ml. of saturated sodium chloride solution, dried for 30 minutes over anhydrous magnesium sulfate, and filtered; the solvent is evaporated. The residue is distilled through a 6-in. Vigreux column using an oil bath maintained at 190° to give 26–29 g. (47–52%) of the product, b.p. 145–155° (Notes 4, 5).

2. Notes

1. Eastman Organic Chemicals practical grade methallyl chloride was distilled (b.p. 70–71°); Union Carbide Chemicals Co. 2,4-pentanedione was distilled (b.p. 134.5–135.5°).

2. Commercial grade absolute ethanol was dried over Linde 3A molecular sieves.

3. At this point most of the ethyl acetate, which is formed as a by-product of the reaction, also is removed.

4. The checkers used a 2-ft. spinning-band column at 200 mm. and observed b.p. 110–111.5°.

5. In the distillation residue (5.7–6.3 g.) remain other by-products, presumably 1,1-dimethallyl-2-propanone, 3-methallyl-2,4-pentanedione, and 3,3-dimethallyl-2,4-pentanedione (indicated by vapor phase chromatography). The checkers carried out v.p.c. analyses using an 8-ft. column of 5% silicone oil XE-60 on Diatoport S at 100° for analysis of the distillate and 175° for analysis of the residue.

3. Methods of Preparation

5-Methyl-5-hexen-2-one has been prepared by alkylation of acetoacetic ester with methallyl chloride, followed by cleavage; the overall yield in the two steps was 51%.[2]

4. Merits of the Preparation

The present procedure, which is characterized by its extreme simplicity, has been employed to prepare various ketones of type RCH_2COCH_3 from 2,4-pentanedione,[3] as indicated in Table I.

TABLE I

Alkylation and Cleavage of 2,4-Pentanedione

Alkyl Halide	Ketone	% Yield
Benzyl chloride	4-Phenyl-2-butanone	73
o-Bromobenzyl bromide	4-(*o*-Bromophenyl)-2-butanone	75
m-Bromobenzyl bromide	4-(*m*-Bromophenyl)-2-butanone	78
o-Chlorobenzyl chloride	4-(*o*-Chlorophenyl)-2-butanone	78
m-Chlorobenzyl bromide	4-(*m*-Chlorophenyl)-2-butanone	65
p-Chlorobenzyl bromide	4-(*p*-Chlorophenyl)-2-butanone	62
m-Fluorobenzyl chloride	4-(*m*-Fluorophenyl)-2-butanone	60
m-Nitrobenzyl chloride	4-(*m*-Nitrophenyl)-2-butanone	65
α-Chloromethylnaphthalene	4-(α-Naphthyl)-2-butanone	61
Phenacyl chloride	1-Phenyl-1,4-pentanedione	55
n-Butyl iodide	2-Heptanone	60

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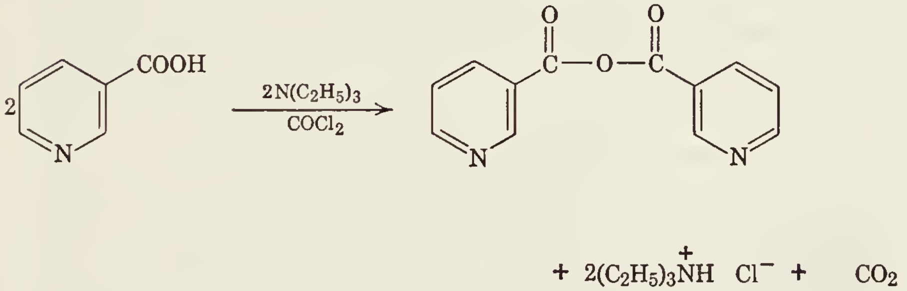
NICOTINIC ANHYDRIDE



Submitted by Heinrich Rinderknecht and Morris Gutenstein[1]
Checked by Walter K. Sosey, Wayland E. Noland,
and William E. Parham

1. Procedure

Nicotinic acid (10 g., 0.081 mole) (Note 1) and anhydrous benzene (275 ml.) (Note 2) are placed in a 500-ml. three-necked, round-bottomed flask (Note 3) fitted with a sealed Hershberg stirrer, a dropping funnel with a pressure-equalizing tube, and a stillhead connected to a condenser. In order to remove traces of moisture introduced with the nicotinic acid the mixture is heated until about 75 ml. of benzene has distilled. The stillhead is replaced by a Claisen head fitted with a thermometer and a calcium chloride tube, and the mixture is cooled to 5° by stirring in an ice bath. To the cold suspension of nicotinic acid is added all at once 8.65 g. (0.086 mole, 5% excess) of triethylamine (Note 4). The resulting clear solution is stirred with continued cooling while 34 g. of a 12.5% solution of phosgene (0.043 mole, 5% excess) in benzene (Note 5) is added through the dropping funnel. The rate of addition is regulated so that the temperature of the reaction mixture does not exceed 7°. Triethylamine hydrochloride precipitates immediately. After the addition of phosgene the mixture is stirred at room temperature for 45 minutes, heated to the boiling point, and filtered under slightly reduced pressure (Note 6) while hot. The triethylamine hydrochloride cake (Note 7) is washed on the filter with three 25-ml. portions of warm benzene (60°). The combined filtrate and washes are transferred to a 500-ml. round-bottomed flask and evaporated to dryness on a rotary evaporator at low temperature and pressure. The dry residue is simmered with 75 ml. of anhydrous benzene (Note 2), and the mixture is filtered while hot. The triethylamine hydrochloride cake (Note 7) is washed with two 5-ml. portions of cold benzene, and the filtrate and washes are allowed to stand at 20° for 2–3 hours. The crystalline product is collected on a filter, washed with two 4-ml. portions of cold anhydrous benzene, and dried in a vacuum. The yield of nicotinic anhydride, m.p. 122–125° (Note 8), is 6.25 g. (68%). The combined filtrate and washes are evaporated to dryness on a rotary evaporator. The residue is simmered with 175 ml. of a mixture of benzene and cyclohexane (2:3) (Note 2), and a small amount of insoluble material is removed by filtration of the hot mixture (Note 6). The filtrate is stored at 5° for 18 hours (Note 9); the crystalline deposit is collected, washed with 3 ml. of cold benzene-cyclohexane mixture, and dried in a vacuum. An additional 2.4 g. (25%) of colorless product, m.p. 122–123°, is thus obtained. The total yield of nicotinic anhydride is 8.05–8.65 g. (87–93%).

2. Notes

1. Nicotinic acid supplied by Matheson, Coleman and Bell yielded a colorless anhydride; U.S.P. grade material gave a slightly buff-colored product.

2. Benzene and cyclohexane are freshly distilled and stored over sodium wire or calcium hydride.

3. Nicotinic anhydride is extremely sensitive to moisture; all glassware is therefore dried overnight in an oven at 200° before use.

4. Triethylamine is freshly distilled and stored over potassium hydroxide pellets.

5. A 12.5% solution of phosgene in benzene is available from Matheson, Coleman and Bell.

6. It is essential to carry out filtration under only slightly reduced pressure in order to minimize evaporation, cooling, and crystallization in the filter plate and funnel.

7. The yield of triethylamine hydrochloride obtained in this and subsequent extractions amounts to over 96% of that expected.

8. Melting points were determined in capillary tubes and are corrected. Reported:[2] 123–126°.

9. Rigorously anhydrous conditions are essential throughout this procedure and the flask must be air-tight.

3. Methods of Preparation

The present method is that described by Rinderknecht and Ma.[3] It is equally applicable to a variety of other heterocyclic, aromatic, and aliphatic anhydrides.[4, 5] Nicotinic anhydride was first prepared by reaction of nicotinoyl chloride with sodium nicotinate,[6, 7] and more recently by reaction of potassium nicotinate with oxalyl chloride in anhydrous benzene.[2]

4. Merits of the Preparation

The present method of preparing anhydrides is distinguished from other procedures by its simplicity and high yield. It avoids the two-phase reaction systems of older methods and the need for often inaccessible and highly sensitive acid chlorides. The only nongaseous by-product, triethylamine hydrochloride, is readily removed from the reaction mixture and leaves, in nearly quantitative yield, a solution of product suitable for further reaction or isolation.

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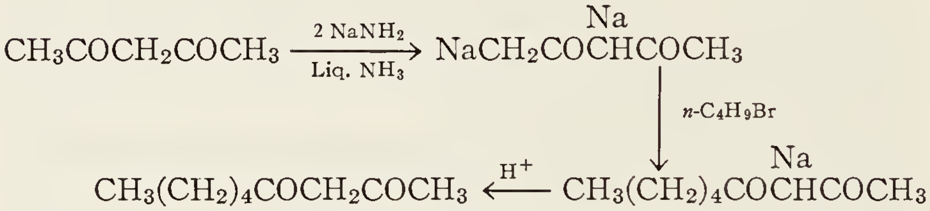
2,4-NONANEDIONE



$$CH_3COCH_2COCH_3 \xrightarrow[\text{Liq. } NH_3]{2\ NaNH_2} NaCH_2CO\overset{Na}{C}HCOCH_3$$

$$\big\downarrow n\text{-}C_4H_9Br$$

$$CH_3(CH_2)_4COCH_2COCH_3 \xleftarrow{H^+} CH_3(CH_2)_4CO\overset{Na}{C}HCOCH_3$$

Submitted by K. Gerald Hampton, Thomas M. Harris, and Charles R. Hauser[1]
Checked by Eugene Gosselink and Peter Yates

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to ammonia.

A suspension of sodium amide (1.10 moles) in liquid ammonia is prepared in a 1-l. three-necked flask equipped with an air condenser (Note 1), a ball-sealed mechanical stirrer, and a glass stopper. In the preparation of this reagent commercial anhydrous liquid ammonia (800 ml.) is introduced from a cylinder through an inlet tube. To the stirred ammonia is added a small piece of sodium. After the appearance of a blue color a few crystals of ferric nitrate hydrate (about 0.25 g.) are added, followed by small pieces of freshly cut sodium until 25.3 g. (1.10 moles) has been added. After the sodium amide formation is complete (Note 2), the glass stopper is replaced by a pressure-equalizing dropping funnel containing 60.0 g. (0.600 mole) of 2,4-pentanedione (Note 3) in 40 ml. of anhydrous ether. The top of the addition funnel is fitted with a nitrogen inlet tube. The reaction flask is immersed at least 3 in. into a dry ice-acetone bath (Note 4), and simultaneously the slow introduction of dry nitrogen through the inlet tube is begun. After the reaction mixture is thoroughly cooled (about 20 minutes), 2,4-pentanedione is added intermittently in small portions (Note 4) over 10 minutes. The cooling bath is removed. After 20 minutes the nitrogen purge is stopped, and 68.5 g. (0.500 mole) of 1-bromobutane (Note 5) in 40 ml. of anhydrous ether is introduced dropwise during 10–20 minutes. The addition funnel is rinsed with a small volume of anhydrous ether, which is added to the reaction mixture. After 30 minutes 400 ml. of anhydrous ether is added, and the ammonia is removed by cautious heating on the steam bath. Crushed ice (200 g.) is added causing a thick slurry to form. Next a mixture of 60 ml. of concentrated hydrochloric acid and 10 g. of crushed ice is added. The reaction mixture is stirred until all solids are dissolved and then is transferred to a separatory funnel, the flask being washed with a little ether and dilute hydrochloric acid. The ethereal layer is separated, and the aqueous layer (Note 6) is further extracted three times with 100-ml. portions of ether. The combined ethereal extracts are dried over anhydrous magnesium sulfate. After filtration and removal of the solvent the residue is distilled through a 12-in. Vigreux column to give 63.0–63.6 g. (81–82%) of 2,4-nonanedione, b.p. 100–103° (19 mm.), as a colorless liquid (Note 7).

2. Notes

1. The checkers used a dry ice condenser during the introduction of ammonia to the reaction flask and replaced it with an air condenser before the addition of sodium.

2. Conversion to sodium amide is indicated by the disappear-

ance of the blue color. This generally requires about 20 minutes.

3. Eastman Organic Chemicals 2,4-pentanedione was dried over potassium carbonate and distilled before use, the fraction boiling at 133–135° at atmospheric pressure being used.

4. The addition of 2,4-pentanedione to liquid ammonia is a highly exothermic process. Also, ammonia vapor reacts with the β-diketone to produce an insoluble ammonium salt, which tends to clog the tip of the addition funnel. Cooling the reaction mixture in dry ice-acetone reduces the vigor of the reaction and minimizes the clogging of the addition funnel. The 2,4-pentanedione should be added in spurts which fall on the surface of the reaction mixture rather than on the wall of the flask.

5. Eastman Organic Chemicals 1-bromobutane was used without purification.

6. The aqueous layer should be acidic to litmus paper. If it is basic, indicating that the ammonia was not completely removed from the reaction mixture, more hydrochloric acid should be added until an acidic test is obtained.

7. A small forerun of 2,4-pentanedione, b.p. 32–100° (19 mm.), is obtained. The purity of the product may be demonstrated by gas chromatography on a 2-ft. column packed with silicone gum rubber (F and M Scientific Co., Avondale, Pennsylvania) programmed linearly from 100° to 300°. The chromatogram obtained is a single sharp peak. The three conceivable impurities, 2,4–pentanedione, 3-butyl-2,4-pentanedione, and 6,8-tridecanedione, would have been observed under these conditions if they had been present.

3. Methods of Preparation

The method described is that of Hampton, Harris, and Hauser[2] and is an improvement over the earlier procedures[3, 4] of Hauser and co-workers, which employed potassium amide. 2,4-Nonanedione has been prepared by the condensation of ethyl caproate with acetone in the presence of sodium hydride (54–80%),[5, 6] and by the acylation of ethyl acetoacetate followed by cleavage and decarboxylation (51%).[7] Other preparations include the acetylation of 2-heptanone with ethyl acetate and sodium amide (61%),[8] the acetylation of 1-heptyne with acetic anhydride and boron fluoride (42%),[9] and the sulfuric acid-catalyzed hydration of 3-nonyn-2-one.[10] Low yields (6–7%) of 2,4-nonanedione were obtained by the acetylation of 2-heptanone with acetic anhydride and boron fluoride,[11] and by the pyrolysis of the enol acetates of 2-heptanone.[12] The last two methods afforded substantial amounts of the isomeric 3-butyl-2,4-pentanedione.

4. Merits of the Preparation

This procedure represents a novel, convenient, and fairly general method for preparing higher β-diketones. By this method the submitters have alkylated 2,4-pentanedione at the 1-position with methyl iodide to give 2,4-hexanedione (59–65%) and with *n*-octyl bromide to give 2,4-tridecanedione (66–79%).[2] Alkylation at the 3-position is not observed, and little or no 1,5-dialkylation occurs. By similar procedures employing potassium amide, 2,4-pentanedione has also been alkylated with benzyl chloride,[3, 4] allyl bromide,[4] *n*-heptyl bromide,[4] and isopropyl bromide.[4] Numerous other β-diketones have been alkylated similarly. They include benzoylacetone,[3] 6-phenyl-2,4-hexanedione,[4, 13] 2-acetylcyclopentanone,[13] 2-acetylcyclohexanone,[13] and 2,4-tridecanedione.[4] In contrast to 2,4-pentanedione, these β-diketones may be added readily to the liquid ammonia solution without employing a dry ice cooling bath.

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OCTANAL

$$n\text{-}C_8H_{17}I + (CH_3)_3N{\rightarrow}O \xrightarrow[CHCl_3]{} n\text{-}C_7H_{15}CHO + (CH_3)_3\overset{+}{N}H \quad I^-$$

Submitted by Volker Franzen[1]
Checked by Claibourne Smith and V. Boekelheide

1. Procedure

To a solution of 30 g. (0.4 mole) of anhydrous trimethylamine oxide (Note 1) in 100 ml. of dry chloroform placed in a 250-ml. three-necked, round-bottomed flask fitted with a reflux condenser, a stirrer, and a dropping funnel with protection against moisture is added 48.0 g. (0.2 mole) of *n*-octyl iodide (Note 2) dropwise with stirring. At the beginning of the addition the flask is warmed to 40–50° on a steam bath to initiate the reaction. The start of the reaction can be recognized by the evolution of heat, and the rate of addition can then be adjusted to maintain the temperature around 50°. Overall the addition requires about 20–30 minutes. When addition is complete, the solution is boiled under reflux for another 20 minutes. Then the solution is cooled, and 110 ml. of $2N$ aqueous sulfuric acid solution is added with stirring. The chloroform layer is separated and washed successively with water, $2N$ aqueous sodium carbonate solution, and again with water. After the chloroform solution has been dried over sodium sulfate, it is concentrated under reduced pressure, and then the residue is distilled. The first distillation (Note 3) is carried out at atmospheric pressure and gives 12.0–12.5 g. of a crude oil, b.p. 155–165°. Redistillation using a simple Vigreux column gives 10.6–11.0 g. (41.5–43%) of a colorless oil, b.p. 69–71° (19 mm.), n^{26}_{D} 1.4167.

2. Notes

1. Trimethylamine oxide is normally available as a hydrate, and for the present preparation it is necessary to convert it to its anhydrous form. A convenient way of doing this is as follows. A solution of 45.0 g. of trimethylamine oxide dihydrate (supplied by Beacon Chemicals) is dissolved in 300 ml. of warm dimethylformamide and placed in a three-necked flask set up for distillation. At atmospheric pressure the flask is heated and solvent distilled off until the boiling point reaches 152–153°. Then the pressure is reduced using a water aspirator, and the remainder of the solvent is distilled. At the end of the distillation the temperature of the bath is slowly raised to 120°. The residual anhydrous trimethylamine oxide (30 g.) can be dissolved in 100 ml. of chloroform and may remain in the same flask for use in the present preparation.

2. In place of *n*-octyl iodide other derivatives such as *n*-octyl bromide, *n*-octyl *p*-toluenesulfonate, and *n*-octyl chlorosulfonate can be substituted; the submitter reports that the yields of octanal in these cases are comparable.

3. At this stage the product is a waxy semisolid, presumably a trimer or polymer of octanal, and the higher temperature of an atmospheric distillation is needed to generate the monomeric octanal.

3. Methods of Preparation

Octanal has been prepared by the reduction of caprylonitrile with hydrogen chloride and stannous chloride,[2] by the passage of a mixture of caprylic acid and formic acid over titanium dioxide [3] or manganous oxide,[4] by dehydrogenation of 1-octanol over copper,[5] and by oxidation of 1-octanol.[6]

4. Merits of the Preparation

The conversion of alkyl halides to aldehydes is a synthetic step of broad utility. Earlier procedures for such conversions involving the use of dimethyl sulfoxide [7] or pyridine N-oxide [8] have worked best with activated alkyl halides, although Kornblum has described a modification of the dimethyl sulfoxide procedure for use with ordinary aliphatic halides.[9] The present procedure using trimethylamine oxide avoids some of the complicating side reactions of pyridine N-oxide and is useful with ordinary aliphatic halides.

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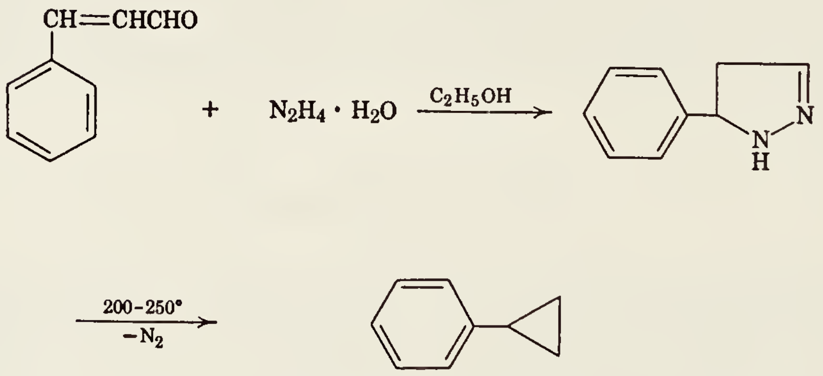
PHENYLCYCLOPROPANE

(Benzene, cyclopropyl-)



Submitted by R. J. PETERSEN and P. S. SKELL [1]
Checked by THOMAS R. LYNCH and PETER YATES

1. Procedure

Caution! This reaction should be carried out behind a safety screen.

A 1-l. three-necked flask is fitted with a reflux condenser, an addition funnel, and a thermometer. It is charged with 450 ml. of 95% ethanol, 230 ml. (236 g.) of 85% hydrazine hydrate (Note 1), and several porcelain boiling chips. The solution is brought to reflux with a heating mantle. Cinnamaldehyde (200 g., 1.51 moles) (Note 2) is added dropwise over a period of 45 minutes to the refluxing solution, while the mixture turns orange because of the formation of cinnamalazine in a side reaction (Note 3). After an additional 30 minutes at reflux, the flask is fitted with a simple takeoff head, and ethanol, water, and hydrazine hydrate are slowly removed by distillation. After approximately 3 hours the pot temperature rises to 200°, and phenylcyclopropane begins to codistil with the last of the hydrazine hydrate (Note 4). The distillate from this point is collected in a 250-ml. receiver, the main fraction coming over at 170–80°. When the pot temperature exceeds 250°, the decomposition is essentially complete (Notes 5, 6).

The crude, cloudy distillate (110–130 g.) is washed twice with 100-ml. portions of water and dried over anhydrous potassium carbonate. Distillation at reduced pressure, b.p. 60° (13 mm.), 79–80° (37 mm.), through a 12-in. Vigreux column gives phenylcyclopropane pure enough for most purposes; yield 80–100 g. (45–56%), n^{25}_{D} 1.5309.

2. Notes

1. Matheson, Coleman and Bell technical grade 85% hydrazine hydrate was used.

2. Eastman Organic Chemicals cinnamaldehyde gave satisfactory results. If colorless crystals are present in the neck of the bottle or on the walls above the liquid, the cinnamaldehyde is seriously contaminated with cinnamic acid and should be distilled before use. A small amount of cinnamic acid apparently does not affect the yield of phenylcyclopropane.

3. Reversal of the addition procedure results in formation of cinnamalazine as a major product.

4. Earlier investigators employed strong bases (sodium hydroxide, potassium hydroxide) or platinum on asbestos to

catalyze the decomposition of 5-phenylpyrazoline. These catalysts are not necessary and should be avoided because they also cause the reduction of cinnamalhydrazone to propenylbenzene. Phenylcyclopropane can be freed from propenylbenzene only with great difficulty.

5. The checkers found in a full-scale run that the pot temperature had to be raised to close to 250° before the onset of reaction, which was then very vigorous.

6. Pyrazoline vapors are known to be rather flammable. It is advisable, therefore, to cool the pyrolysis flask somewhat before dismantling the apparatus. The syrupy residue in the flask sets to a hard mass on cooling; it can be removed by heating under dimethylformamide on a steam bath overnight.

3. Methods of Preparation

Phenylcyclopropane has been prepared by the base-catalyzed decomposition of 5-phenylpyrazoline (33%),[2] by the reaction of 1,3-dibromo-1-phenylpropane with magnesium (68%),[3] and by the reaction of 3-phenylpropyltrimethylammonium iodide with sodium amide in liquid ammonia (80%).[4] However, the method frequently used at present is the reaction of styrene with the methylene iodide-zinc reagent (32%).[5]

4. Merits of the Preparation

The procedure outlined is much quicker and simpler than previous methods. Starting materials are readily available, and the preparation can be run on any scale in the length of a day. Because exclusion of a basic catalyst eliminates the Wolff-Kishner reduction of the cinnamalhydrazone, separation of the 5-phenylpyrazoline from cinnamalhydrazone, or of phenylcyclopropane from propenylbenzene, does not have to be effected. The present procedure can also be used to convert other ring-substituted cinnamaldehydes to the corresponding arylcyclopropanes.

1. Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania.

2. S. G. Beech, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).
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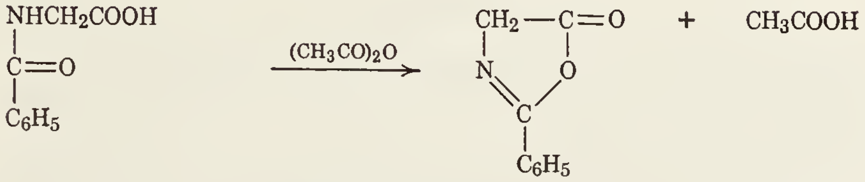
2-PHENYL-5-OXAZOLONE

(2-Phenyl-2-oxazolin-5-one)



Submitted by G. E. VandenBerg,[1] J. B. Harrison,[2]
H. E. Carter,[2] and B. J. Magerlein [1]
Checked by William G. Dauben, Noel Vietmeyer,
and Steven A. Schmidt

1. Procedure

A mixture of 537 g. (3 moles) of hippuric acid (Note 1) and 1.6 l. (17 moles) of acetic anhydride is prepared in a 3-l. three-necked, round-bottomed flask fitted with a sealed stirrer, a reflux condenser with a drying tube, a thermometer, and a nitrogen inlet tube (Note 2).

In a nitrogen atmosphere the reaction mixture is heated to 80° *on a water bath* over a period of 40 minutes with stirring. The solids slowly dissolve, and a yellow-orange solution results (Note 3). The reaction mixture is cooled to 5°, and the reflux condenser is turned downward for distillation. The condenser is cooled with a circulating fluid maintained at −20° to −40° (Note 4). The receiver is immersed in dry ice and acetone. At 1–3 mm. pressure, 1.5 l. of distillate is collected while the distillation flask is kept in a water bath maintained at 50° (Note 5). A capillary tube is used to bubble nitrogen through the reaction mixture to ensure good agitation. The distillation residue is dissolved in 1 l. of *t*-butanol, the solution scratched to encourage crystallization, and it is refrigerated overnight. The crystals are collected by filtration (Note 2). The filter cake is washed with a minimum volume of *t*-butanol and then with Skellysolve B (Note 6) or hexane. The moist cake is slurried with Skellysolve B or hexane under a nitrogen atmosphere (Note 7), filtered, and dried to constant weight under vacuum at ambient temperature. The yield of light buff to yellow crystals, m.p. 89–92°, is 320–328 g. (66–68%).

2. Notes

1. The checkers ran the reaction on one-fifth scale.
2. Exposure to air produces a pink to red product of lower melting point and purity.
3. Temperature control is important in order to obtain a high yield of light-colored product. Prolonged heating at 80° is to be avoided.
4. Acetone, cooled by passing through a copper coil placed in a dry ice-acetone bath, may be circulated through the condenser. If a temperature lower than −40° is used, the distillate will freeze in the condenser.
5. This distillate should be collected within about 1 hour, as longer distillation time diminishes the yield.
6. A saturated hydrocarbon fraction, b.p. 60–71°, available from the Skelly Oil Company, Kansas City, Missouri.
7. Alternatively, the moist cake may be recrystallized by dissolving in hot *t*-butanol (about 800 ml.) and diluting with Skellysolve B. The yield is then about 40–50% and the melting point about the same as that of the reslurried product.

3. Methods of Preparation

This procedure is a modification of the original method of preparation of 2-phenyl-5-oxazolone [3] which has since appeared in the literature in various forms.[4–6] In addition to the use of acetic anhydride, the cyclization of hippuric acid to 2-phenyl-5-oxazolone has been described using phosphorus tribromide [7] and N,N′-dicyclohexylcarbodiimide.[8]

4. Merits of the Preparation

This procedure offers a reproducible method for the preparation of 2-phenyl-5-oxazolone, which is not commercially available. It illustrates that strict attention to detail often smooths out an erratic procedure. 2-Phenyl-5-oxazolone is, of course, an important intermediate in the synthesis of α-amino acids and related materials.[6]

1. Research Laboratories, The Upjohn Company, Kalamazoo, Michigan.
2. University of Illinois, Urbana, Illinois.
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REDUCTION OF ORGANIC HALIDES. CHLOROBENZENE TO BENZENE

$$C_6H_5Cl + (CH_3)_2CHOH + Mg \longrightarrow C_6H_6 + (CH_3)_2CHOMgCl$$

Submitted by D. Bryce-Smith and B. J. Wakefield[1]
Checked by William G. Dauben and Louis E. Friedrich

1. Procedure

To a 250-ml. round-bottomed flask fitted with a glass-blade stirrer, a pressure-equalizing dropping funnel, a thermometer, and a reflux condenser equipped with a nitrogen bubbler (Note 1) are added 6.0 g. (0.25 mole) of magnesium powder (Note 2), 50 ml. of decahydronaphthalene (Note 3), and a crystal of iodine. The flask is swept with nitrogen, and a nitrogen atmosphere is maintained throughout the reaction. The mixture is heated to reflux without stirring, and from the dropping funnel there is added slowly one-fifth of a solution of 11.3 g. (0.1 mole) of chlorobenzene (Note 4) and 9.0 g. (0.15 mole) of dry 2-propanol. Reaction is almost immediately apparent in the region of the iodine crystal, and as the reaction becomes progressively more vigorous (*ca.* 15 minutes) the stirrer is started and the external heating is reduced (Note 5). The remainder of the chlorobenzene solution is added over a 30-minute period; this rate of addition causes the mixture to reflux gently without external heating. An additional 25 ml. of decahydronaphthalene is added to facilitate the stirring, and the mixture is heated under reflux for one additional hour.

To the cooled mixture 6*N* hydrochloric acid is added dropwise with stirring, until no solid remains. The organic layer is separated, washed four times with 30-ml. portions of water (Note 6), dried over powdered calcium chloride (Note 7), and distilled through a 1 × 15 cm. column packed with Fenske helices (Note 8). The yield of benzene is 5.5–6.5 g. (70–83%), b.p. 80–82°, $n^{20}\text{D}$ 1.5007. The fraction boiling at 82–180° contains no unreacted chlorobenzene (Notes 9, 10, 11).

2. Notes

1. To minimize loss of volatile products such as benzene, it is advisable to employ a dry ice condenser on top of the conventional condenser.

2. Magnesium powder (Grade 4) from Magnesium Elektron, Inc., 610 Fifth Avenue, New York 20, New York, or from Magnesium Elektron Ltd., Manchester, England, was employed within six months of the date of its grinding by the manufacturer. The use of older or coarser material may lead to lengthened induction periods, particularly when chlorides are used.

3. Freshly distilled decahydronaphthalene was used. With the more easily reduced halides, and where the boiling point of the neutral reduction product was close to that of decahydronapthalene, an excess of 2-propanol was used as the reaction medium. Other hydrocarbons and secondary or tertiary alcohols may be employed for convenience in particular reductions. Diethyl ether and tetrahydrofuran were not found to be generally suitable media.

4. The checkers found it necessary to distil the chlorobenzene just before use.

5. When there is no sustained reaction after 10 minutes, initiation can often be accomplished by the addition of another crystal of iodine (no stirring) and/or a small amount of an easily reduced halide such as 1-bromobutane.

6. These washings remove the bulk of the 2-propanol.

7. This drying also removes the last traces of 2-propanol.

8. The checkers used a Nester-Faust 44-cm. spinning-band column.

9. This procedure has been used to effect the following reductions at *ca.* 150°: bromobenzene to benzene (89%), iodobenzene to benzene (95%), 1-chlorobutane to *n*-butane (95%), 2-chloro-2-methylbutane to 2-methylbutane (32%), and isopropyl chloroacetate to isopropyl acetate (63%).

10. The following reductions have been carried out at 80° with the use of an excess of 2-propanol as the reaction medium (see Note 3): carbon tetrachloride to methane (47%), 1-bromonaphthalene to naphthalene (90%), β-bromostyrene to styrene (72%), *p*-bromoaniline to aniline (61%), *p*-bromophenol to phenol (66%), and monochloroacetone to acetone (30%).

11. Certain halides, notably fluorides, are comparatively inert under these reaction conditions. In such cases the *entrainment method* can be used, and reduction can be accomplished in the presence of a reactive halide such as 1-bromonaphthalene or 1-bromobutane. Also with certain halides, such as chlorocyclohexane, the tendency for dehydrohalogenation is diminished by the use of such entraining agents.

A typical example is the following reduction of chlorocyclohexane to cyclohexane. The general procedure is employed using 8.0 g. (0.33 mole) of magnesium powder in decahydronaphthalene (50 ml. + 20 ml.) and a solution of 6.0 g. (0.05 mole) of chlorocyclohexane, 10.4 g. (0.05 mole) of 1-bromonaphthalene, and 18 g. (0.3 mole) of 2-propanol. The product fraction, b.p. 78–80°, is a mixture of 3.5 g. (83%) of cyclohexane and 0.4 g. (10%) of cyclohexene. The olefin is removed by treatment with concentrated sulfuric acid in the usual manner.

Under the foregoing conditions, fluorocyclohexane gives cyclohexane (33%), and benzotrifluoride gives toluene (10%); fluorobenzene is inert.

3. Methods of Preparation

The present procedures are based on those briefly described by the submitters in conjunction with E. T. Blues,[2] and are based on the observation that magnesium does not, under normal conditions, readily react with secondary and tertiary alcohols in the absence of a halogen or an organic halide; little or no hydrogen is evolved during the reduction. Magnesium reacts readily with primary alcohols, evolving hydrogen, and the system is much less active in the reduction of organic halides. 2-Propanol is recommended as a general-purpose alcoholic component, but other secondary and tertiary alcohols can also be employed.

4. Merits of the Preparation

Reduction with magnesium and 2-propanol provides a simple and effective procedure for the reduction of alkyl and aryl chlorides, bromides, and iodides; with an entraining agent some alkyl fluorides are attacked. Groups such as amino, phenolic hydroxyl, ester carbonyl, and ethylenic linkages have not interfered. Nitro compounds must be absent as they inhibit the reaction with magnesium. Many carbonyl compounds, for example, *p*-bromobenzophenone, undergo much simultaneous reduction of the carbonyl groups, but acetone was obtained in fair yield from chloroacetone.

1. Department of Chemistry, The University, Reading, England.
2. D. Bryce-Smith, B. J. Wakefield, and E. T. Blues, *Proc. Chem. Soc.*, 219 (1963).

m-THIOCRESOL[1]

WARNING

Diazonium xanthates ($ArN{=}NSCSOC_2H_5$) can detonate, and this procedure should be followed carefully to ensure decomposition of the xanthate as it is formed. Under no circumstances should the diazonium solution and the potassium ethyl xanthate be mixed cold and the mixture subsequently heated. A severe detonation has been reported when such a procedure was employed during the preparation of thiocresol.

It has been observed[2] that the dropwise addition of an aqueous solution of potassium ethyl xanthate to a cold (0°) aqueous solution of diazotized orthanilic acid results in the immediate loss of nitrogen when a trace of nickel ion is present in the stirred diazonium solution.[3] The catalyst can be added as nickelous chloride or simply by using a nichrome wire stirrer. When no nickel ion is added and a glass stirrer is employed, the diazonium xanthate precipitates and requires heat (32°) to effect decomposition.

The use of a nichrome stirrer or a catalytic amount of nickel ion is recommended[1] for such reactions to minimize the accumulation of diazonium xanthate; however, the catalytic role of nickel ion has not been explored with other diazonium salts.

1. *Org. Syntheses*, Coll. Vol. **3**, 809 (1955).
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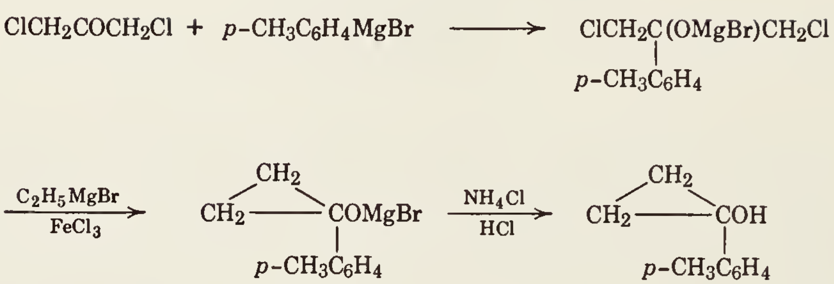
1-*p*-TOLYLCYCLOPROPANOL



Submitted by C. H. DePuy and R. A. Klein[1]
Checked by O. Aniline and K. B. Wiberg

1. Procedure

In a dry 3-l. three-necked, round-bottomed flask fitted with an efficient reflux condenser, a stirrer, a Y-tube holding a 1-l. and a 250-ml. addition funnel, and protected from moisture by calcium chloride tubes is placed 5.76 g. (0.237 mole) of magnesium turnings barely covered by anhydrous ether. *p*-Bromotoluene (40 drops) and ethyl bromide (20 drops) are added, and the reaction starts immediately. *p*-Bromotoluene (35.0 g., 0.205 mole) in 200 ml. of anhydrous ether is added at such a rate that reflux is maintained. To the resultant solution of *p*-methylphenylmagnesium bromide is added, over a 1-hour period, a solution of 25.4 g. (0.200 mole) of dichloroacetone in 200 ml. of anhydrous ether.

At the same time, in a separate 2-l. three-necked, round-bottomed flask equipped with reflux condenser, stirrer, and addition funnel, ethylmagnesium bromide is prepared from 128.6 g. (1.18 moles) of ethyl bromide and 30 g. (1.23 moles) of magnesium in 800 ml. of anhydrous ether. When the reaction is complete, the addition funnel is replaced by a rubber stopper containing a short glass tube, and the reflux condenser is replaced by an exit tube lightly plugged with a small amount of glass wool. The Grignard reagent solution is forced, under mild nitrogen pressure, through the glass wool plug into the 1-l. addition funnel (Note 1). In the 250-ml. addition funnel is placed a filtered solution of 2.5 g. (0.0154 mole) of anhydrous ferric chloride in 200 ml. of anhydrous ether. Stirring is resumed, and the two solutions are simultaneously added to the dichloroacetone-*p*-methylphenylmagnesium bromide solution over a 2-hour period (Note 2). Stirring is continued for an additional 14 hours under dry nitrogen.

The reaction mixture is added to a slurry of 1500 g. of ice and 600 ml. of 2*N* hydrochloric acid saturated with ammonium chloride. The ether layer is separated, and the aqueous layer is extracted three times with 200-ml. portions of ether. The combined organic layers are washed with three 200-ml. portions of water until a neutral reaction is obtained with litmus and the wash water is free of chloride. The solution is dried over anhydrous magnesium sulfate and stored in a refrigerator. After evaporation of the ether, the residue is distilled at a low pressure through a short Vigreux column (Note 3). The fraction, b.p. 70–78° (0.4 mm.) (oil bath 100–135°), is collected to give 15–17 g. (51–57%) of the crude carbinol which crystallizes upon standing in an ice box. The product is recrystallized from pentane (4 g. per g. of alcohol) in an ice-salt mixture to give the pure alcohol, m.p. 38–39°.

2. Notes

1. Since the ethyl Grignard reagent is used in large excess, no special precautions need to be taken in the transfer to prevent the loss of small amounts.

2. Large volumes of gas are generated, primarily ethane and ethylene, from the disproportionation of the ethyl radicals produced in the reaction of ethylmagnesium bromide with ferric chloride. The reaction should be carried out in an efficient hood, or else a tube should be run from the top of the reflux condenser to a hood.

3. 1-Arylcyclopropanols readily rearrange to propiophenones under the influence of acids and bases. In carrying out the distillation, care must be taken that the apparatus is clean and neutral.

3. Methods of Preparation

The method is that of DePuy and co-workers.[2] No other syntheses of 1-arylcyclopropanols have been reported.

4. Merits of the Preparation

The procedure can be adapted to the preparation, in comparable yield, of a variety of 1-substituted cyclopropanols, alkyl as well as aryl.

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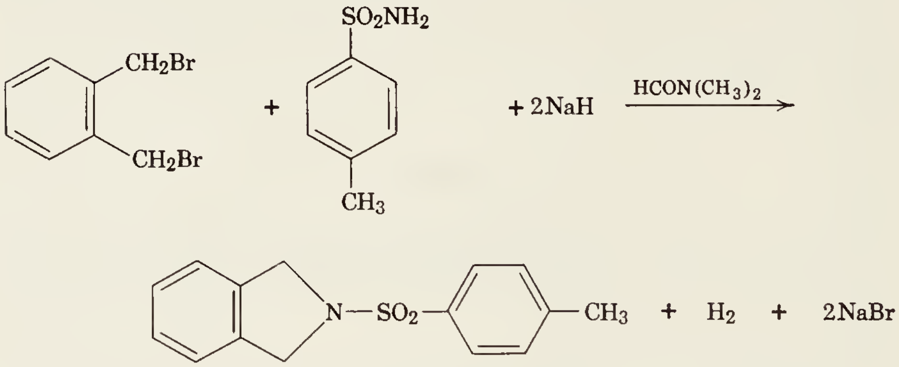
1. Department of Chemistry, University of Colorado, Boulder, Colorado.
2. C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

2-(*p*-TOLYLSULFONYL)DIHYDROISOINDOLE

(Isoindoline, 2-*p*-tolylsulfonyl-)



Submitted by J. Bornstein and J. E. Shields [1]
Checked by Rosetta McKinley and R. E. Benson

1. Procedure

Caution! This reaction should be carried out in a good hood because hydrogen is evolved and o-xylylene dibromide is a powerful lachrymator (Note 6).

A 1-l. three-necked flask is fitted with an efficient stirrer (Note 1), thermometer, condenser, and a pressure-equalizing dropping funnel that carries an inlet for admission of dry nitrogen. The entire apparatus is dried by warming with a soft flame as a brisk stream of nitrogen is passed through the system. The flow of nitrogen is reduced to a slow stream, and in the cooled flask are placed 18.9 g. (0.42 mole) of 53% sodium hydride dispersed in mineral oil (Note 2) and 60 ml. of purified dimethylformamide (Note 3). The mixture is stirred at room temperature and a solution of 34.2 g. (0.20 mole) of *p*-toluenesulfonamide (Note 4) in 100 ml. of purified dimethylformamide is added dropwise over a period of 1 hour. The resulting suspension is stirred at room temperature for 1 hour and then at 60° for an additional hour (Note 5).

A solution of 52.8 g. (0.20 mole) of *o*-xylylene dibromide (Note 6) in 300 ml. of purified dimethylformamide is added dropwise with stirring at such a rate as to maintain a temperature of 60–70° (Note 7). Subsequently the reaction mixture is stirred at room temperature for 3 hours and then poured into 600 ml. of ice water in a 2-l. Erlenmeyer flask. After standing at room temperature overnight the product is collected by suction filtration, pressed on the funnel, and washed twice with 100-ml. portions of water. The crude product is air-dried on filter paper for 2–3 hours and is then dissolved in 1.2 l. of boiling 95% ethanol. The solution is filtered through a heated funnel, and the filtrate is refrigerated overnight. The crystals are collected on a Buchner funnel and washed on the funnel with 100 ml. of cold 95% ethanol. The product is dried over phosphorus pentoxide in a vacuum desiccator. The yield of white crystals of 2-(*p*-tolylsulfonyl)-dihydroisoindole is 41–46 g. (75–84%), m.p. 174–175° (dec.).

2. Notes

1. Either a paddle-type sealed stirrer or a heavy-duty magnetic stirrer is suitable.

2. Sodium hydride was obtained from Metal Hydrides Division of Ventron Corporation, Beverly, Massachusetts.

3. Dimethylformamide, b.p. 152–154°, purchased from Matheson, Coleman and Bell, was stirred for 5 minutes with solid potassium hydroxide, decanted, shaken briefly with lime, filtered, and distilled.

4. Commercial *p*-toluenesulfonamide of high purity was recrystallized from water and dried over phosphorus pentoxide in a vacuum desiccator, m.p. 134–135°.

5. It is necessary to maintain vigorous stirring at this stage to prevent excessive foaming due to the evolution of hydrogen.

6. Precautions to be observed in handling *o*-xylylene dibromide are described in *Org. Syntheses*, Coll. Vol. **4**, 984 (1963). The dibromide was purchased from Eastman Organic Chemicals, recrystallized from 95% ethanol (3 ml./g.), and dried over potassium hydroxide in a vacuum desiccator, m.p. 89–91°.

7. Control of the temperature at this point is critical; a deeply colored product is obtained if the temperature is allowed to exceed 70°. The addition of the dibromide requires about 1 hour.

3. Methods of Preparation

2-(*p*-Tolylsulfonyl)dihydroisoindole has been prepared by alkylation of *p*-toluenesulfonamide with *o*-xylylene dibromide in the presence of sodium methoxide in ethanol.[2, 3]

4. Merits of the Preparation

This is the most practical procedure for the preparation of 2-(*p*-tolylsulfonyl)dihydroisoindole. It is superior to earlier ones [2, 3] because it is more convenient and affords considerably higher yields (*ca.* 80% versus *ca.* 45%).

The method illustrates the ability of the sodium hydride-dimethylformamide system to effect the alkylation of aromatic sulfonamides under mild conditions and in good yield. The method appears to be fairly general. The submitters have prepared N,N-diethyl- and N,N-di-*n*-butyl-*p*-toluenesulfonamide as well as 2-(*p*-tolylsulfonyl)benz[*f*]isoindoline from 2,3-bis-(bromomethyl)naphthalene, and 1-(*p*-tolylsulfonyl)pyrrolidine from 1,4-dichlorobutane; the yield of purified product exceeded 75% in each case.

The reductive cleavage of 2-(*p*-tolylsulfonyl)dihydroisoindole to 1,3-dihydroisoindole constitutes the most convenient synthesis of this heterocyclic compound.[3] The sulfonamide is also useful in the synthesis of isoindole.[4]

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UNSOLVATED *n*-BUTYLMAGNESIUM CHLORIDE

$$CH_3CH_2CH_2CH_2Cl + Mg \xrightarrow{\text{Methylcyclohexane}} CH_3CH_2CH_2CH_2MgCl$$

(Note 1)

Submitted by D. Bryce-Smith and E. T. Blues [1]
Checked by William E. Parham and Siemen Groen

1. Procedure

In a 250-ml. round-bottomed flask fitted with a glass-link or Teflon stirrer, thermometer, reflux condenser with outlet to an oil seal, dropping funnel, and inlet for nitrogen (Notes 2, 3) are placed 3.22 g. of magnesium powder (0.132 mole) (Note 4) having a particle size of 64–76 μ (Notes 5, 6), and 60 ml. of methylcyclohexane (Note 7). The apparatus is flushed with nitrogen. A slow stream of nitrogen is introduced, and the methylcyclohexane is heated to reflux temperature (Note 8).

About one-fifth of a solution of 9.26 g. of 1-chlorobutane (0.1 mole) (Notes 9, 10) in 20 ml. of methylcyclohexane is added to the vigorously stirred refluxing mixture. Reaction commences (gray turbidity) within 2–8 minutes (Notes 5, 11), and the remainder of the halide solution is then added steadily over about 12 minutes to the heated mixture, the rate being adjusted so that the inner temperature of the refluxing mixture does not fall appreciably below 99–100°. Stirring and heating under reflux are continued for an additional 15 minutes. The resulting product contains approximately 0.073 mole (73% yield) of *n*-butylmagnesium chloride as determined either by hydrolysis to *n*-butane (Notes 12, 13) or by titration (Note 14).

2. Notes

1. The empirical formula of *n*-butylmagnesium chloride prepared in methylcyclohexane cannot readily be determined because of the virtual insolubility of the reagent in this medium. The reagent is somewhat more soluble in aromatic media such as toluene or isopropylbenzene, and, although the empirical formula of the solute may initially approach C_4H_9MgCl, there is a tendency for precipitation of magnesium chloride from solution. This process appears to be catalyzed by traces of alkoxides, which are liable to be formed after contact of oxygen with the solution. In practice, products will tend to contain less halogen than is required by the simple formula C_4H_9MgCl. The reagents are associated (see reference 2 for a fuller discussion).

2. The nitrogen used (British Oxygen Co., White Spot) contained about 10 p.p.m. of oxygen and was dried by passage through a glass spiral cooled in acetone and solid carbon dioxide. For the most precise work, the submitters reduced the proportion of oxygen to about 0.1 p.p.m. by scrubbing the nitrogen with chromous chloride solution in a Nilox apparatus (Southern Analytical Ltd., Camberley, Surrey, England).

3. The apparatus should preferably be baked at 120° for several hours immediately before use. The uppermost region of condensing methylcyclohexane should not be cloudy; if it is, a few milliters should be allowed to distil.

4. The yield of *n*-butylmagnesium chloride is increased to 80% (analyzed by evolution of *n*-butane) if twice the stated amount of magnesium is used.

5. Magnesium powder (grade 4, Magnesium Elektron Ltd., Manchester, England) was used within 6 months of its grinding by the manufacturer, and was sieved to the stated particle size. The use of unsieved material often gives results nearly as good, but exact reproducibility is more difficult because of variations of the particle size distribution from sample to sample. In general, the more freshly ground the magnesium, the shorter are the induction periods before reaction and, to a limited extent, the higher are the yields of organomagnesium product.

6. Fresh magnesium turnings for Grignard reaction can be used if suitable powder is unavailable, but initiation of reaction is likely to be prolonged, and the subsequent addition of the halide solution should occupy at least 30 minutes, longer if possible.

7. Methylcyclohexane is purified by shaking with 3 portions of concentrated sulfuric acid, washing successively with water, sodium carbonate solution, and water, drying over calcium sulfate (Drierite), and distilling. The material boiling at 100–101° is used. Other nonsolvating media which can be used are toluene, xylenes, cumene, tetralin, light petroleum (b.p. 80°), decalin, and kerosene; aliphatic media are preferred, for reasons given in references 2, 3, and 4.

8. The rate of flow of nitrogen should be just sufficient to maintain a positive pressure in the apparatus. Too rapid a flow leads to loss of 1-chlorobutane.

9. 1-Chlorobutane is purified with sulfuric acid as for methylcyclohexane (Note 7), dried over calcium chloride, and fractionated. A middle fraction is collected.

10. The yield of product is increased to 81% (analyzed by evolution of *n*-butane) if 0.67 g. (0.0033 mole) of aluminum isopropoxide is added to the suspension of magnesium before addition of the halide solution. Alternatively, an equivalent amount of 2-propanol and iodine (giving 0.01 mole of C_3H_7OMgI) may be added. These modified procedures (particularly the second) also shorten the induction periods and render unnecessary any special drying of the reagents and apparatus and the use of fresh magnesium.

The products in such cases contain complexes between *n*-butylmagnesium chloride and the particular alkoxide employed. With the stated low proportions of alkoxides, these complexes broadly resemble the alkoxide-free materials, but increased proportions of the alkoxide component give complexes having generally decreased chemical reactivity (see references 3 and 4).

11. The reaction generally starts without addition of iodine as an initiator, but the use of a crystal of iodine (no stirring) may occasionally be necessary with "old" magnesium or insufficiently

dried materials or apparatus. A slower rate of addition of 1-chlorobutane gives slightly higher yields; for example, addition over a period of 60 minutes gave yields of 82–87%.

12. The reflux condenser was connected by an adaptor and Teflon tube to a trap of known weight which was cooled by a mixture of acetone and solid carbon dioxide. The flow of nitrogen was stopped, and an excess of water (about 15 ml.) was added dropwise through the dropping funnel to the stirred reaction product. The resulting mixture was heated at the reflux temperature, and the butane was collected in the trap. The weight of butane, b.p. −1° to 0°, was 4.23–4.35 g. (73–76% yield).

13. The submitters have detected traces of *trans*-butene-2 and propylene among the gases (mainly *n*-butane and hydrogen) formed on hydrolysis.

14. Sufficient dry ether (approximately 100 ml.) is added to bring the organomagnesium products into solution. Aliquot portions of the solution are then added to a known volume of standard hydrochloric acid, and the excess acid is determined by titration with standard base. Yields determined in this way tend to be a few percent higher than those determined by collection of *n*-butane (Note 12).

3. Methods of Preparation

The method is an extension of the well-known Grignard synthesis in ethers to the use of nonsolvating media, and is a development of procedures previously reported.[2–6] A version of it has been employed with straight-chain primary alkyl chlorides, bromides, and iodides from C_2 to C_{14},[5–7] and in solvents (or an excess of the halide) which permit reaction temperatures above 120°, with simple aryl halides such as chlorobenzene and 1-chloronaphthalene. Branched-chain primary, secondary, and tertiary alkyl halides, allyl, vinyl, and benzyl halides either fail to react or give extensive side reactions. Better results are reported to be obtained in such cases with the use of catalytic quantities of a mixture of an alkoxide and an ether such as diethyl ether or tetrahydrofuran in a hydrocarbon medium, but the products are not, of course, completely unsolvated.[4]

4. Merits of the Preparation

Unsolvated organomagnesium compounds have been recommended for the synthesis of organometallic derivatives of mercury, boron, aluminum, silicon, germanium, tin, phosphorus, arsenic, and antimony [3, 6, 8] and have been used in procedures for the alkylation of aromatic rings and for the production of various polymerization catalysts.[4, 6, 9]

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SUBJECT INDEX

(*This index comprises material from Volumes 45, 46, and 47 only; for previous volumes see Collective Volumes 1 through 4 and Volume 44.*)

Names in small capital letters refer to the titles of individual preparations. A number in ordinary boldface type denotes the volume. A page number in boldface italics indicates that the detailed preparative directions are given or referred to; entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations.

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